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29 JULY 1999

REC'D 15 SEP 1999  
INVESTOR & PEOPLE

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4  
The Patent Office  
Concept House  
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South Wales  
NP10 8QQ

## PRIORITY DOCUMENT

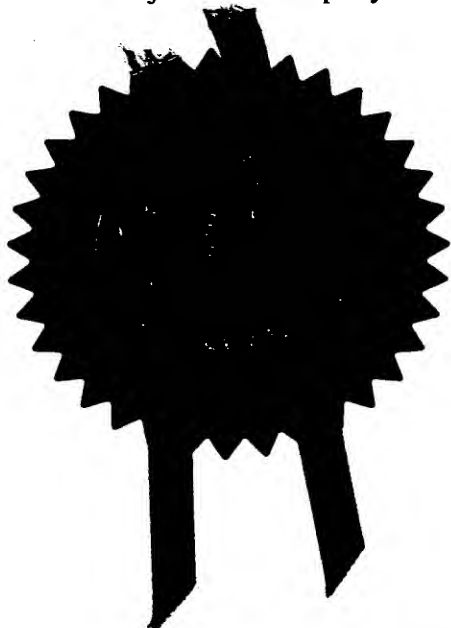
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In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

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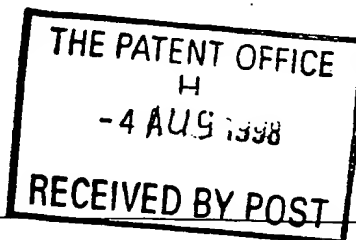
*Andrew Gensy*

Dated 23 August 1999

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# Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)



The Patent Office

Cardiff Road  
Newport  
Gwent NP9 1RH

1. Your reference 98-063

2. Patent application number  
(The Patent Office will fill in this part)

04 AUG 1998

9816837.0

3. Full name, address and postcode of the or of each applicant (*underline all surnames*)  
ZENECA Limited  
15 Stanhope Gate  
LONDON W1Y 6LN, Great Britain  
Patents ADP number (*if you know it*)  
6254007002

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention  
AMIDE DERIVATIVES

5. Name of your agent (*if you have one*)  
TAIT, Brian Steele  
"Address for service" in the United Kingdom to which all correspondence should be sent  
(*including the postcode*)  
Intellectual Property Department  
ZENECA Pharmaceuticals  
Mereside, Alderley Park,  
Macclesfield, Cheshire, SK10 4TG, Great Britain  
Patents ADP number (*if you know it*) 5684600002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and ( <i>if you know it</i> ) the or each application number	Country	Priority application number ( <i>if you know it</i> )	Date of filing ( <i>day / month / year</i> )
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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing ( <i>day / month / year</i> )
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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (*Answer 'Yes' if:*  
a) any applicant named in part 3 is not an inventor, or  
b) there is an inventor who is not named as an applicant, or  
c) any named applicant is a corporate body.  
See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form

Description 55

Claim(s) -

Abstract -

Drawing(s) -

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for preliminary examination and search (Patents Form 9/77)

Request for substantive examination (Patents Form 10/77)

Any other documents (please specify)

11. I/We request the grant of a patent on the basis of this application.

Signature

Lynda May Slack

Date

3 Aug 98

12. Name and daytime telephone number of person to contact in the United Kingdom

Lynda M Slack  
01625 516173

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Notes

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AMIDE DERIVATIVES

This invention concerns certain amide derivatives which are useful as inhibitors of cytokine mediated disease. The invention also concerns processes for the manufacture of the  
5 amide derivatives of the invention, pharmaceutical compositions containing them and their use in therapeutic methods, for example by virtue of inhibition of cytokine mediated disease.

The amide derivatives disclosed in the present invention are inhibitors of the production of cytokines such as Tumour Necrosis Factor (hereinafter TNF), for example  $\text{TNF}\alpha$ , and various members of the interleukin (hereinafter IL) family, for example IL-1, IL-6  
10 and IL-8. Accordingly the compounds of the invention will be useful in the treatment of diseases or medical conditions in which excessive production of cytokines occurs, for example excessive production of  $\text{TNF}\alpha$  or IL-1. It is known that cytokines are produced by a wide variety of cells such as monocytes and macrophages and that they give rise to a variety of physiological effects which are believed to be important in disease or medical conditions  
15 such as inflammation and immunoregulation. For example,  $\text{TNF}\alpha$  and IL-1 have been implicated in the cell signalling cascade which is believed to contribute to the pathology of disease states such as inflammatory and allergic diseases and cytokine-induced toxicity. It is also known that, in certain cellular systems,  $\text{TNF}\alpha$  production precedes and mediates the production of other cytokines such as IL-1.

20 Abnormal levels of cytokines have also been implicated in, for example, the production of physiologically-active eicosanoids such as the prostaglandins and leukotrienes, the stimulation of the release of proteolytic enzymes such as collagenase, the activation of the immune system, for example by stimulation of T-helper cells, the activation of osteoclast activity leading to the resorption of calcium, the stimulation of the release of proteoglycans  
25 from, for example, cartilage, the stimulation of cell proliferation and to angiogenesis.

Cytokines are also believed to be implicated in the production and development of disease states such as inflammatory and allergic diseases, for example inflammation of the joints (especially rheumatoid arthritis, osteoarthritis and gout), inflammation of the gastrointestinal tract (especially inflammatory bowel disease, ulcerative colitis and gastritis),  
30 skin disease (especially psoriasis, eczema and dermatitis) and respiratory disease (especially asthma, bronchitis, allergic rhinitis and adult respiratory distress syndrome), and in the

production and development of various cardiovascular and cerebrovascular disorders such as myocardial infarction, the formation of atherosclerotic plaques, hypertension, platelet aggregation, angina, stroke, reperfusion injury, vascular injury including restenosis and peripheral vascular disease, and, for example, various disorders of bone metabolism such as  
5 osteoporosis (including senile and postmenopausal osteoporosis), Paget's disease, bone metastases, hypercalcaemia, hyperparathyroidism, osteosclerosis, osteoporosis and periodontitis, and the abnormal changes in bone metabolism which may accompany rheumatoid arthritis and osteoarthritis. Excessive cytokine production has also been implicated in mediating certain complications of bacterial, fungal and/or viral infections such  
10 as endotoxic shock, septic shock and toxic shock syndrome and in mediating certain complications of CNS surgery or injury such as neurotrauma and ischaemic stroke. Excessive cytokine production has also been implicated in mediating or exacerbating the development of diseases involving cartilage or muscle resorption, pulmonary fibrosis, cirrhosis, renal fibrosis, the cachexia found in certain chronic diseases such as malignant disease and acquired immune  
15 deficiency syndrome (AIDS), tumour invasiveness and tumour metastasis and multiple sclerosis.

Evidence of the central role played by  $\text{TNF}\alpha$  in the cell signalling cascade which gives rise to rheumatoid arthritis is provided by the efficacy in clinical studies of antibodies of  $\text{TNF}\alpha$  (The Lancet, 1994, 344, 1125 and British Journal of Rheumatology, 1995, 34, 334).

20 Thus cytokines such as  $\text{TNF}\alpha$  and IL-1 are believed to be important mediators of a considerable range of diseases and medical conditions. Accordingly it is expected that inhibition of the production of and/or effects of these cytokines will be of benefit in the prophylaxis, control or treatment of such diseases and medical conditions.

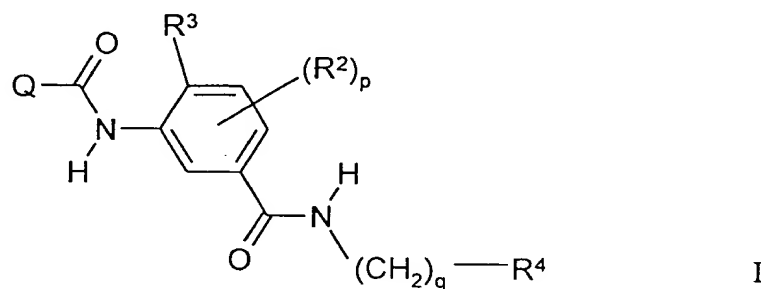
Without wishing to imply that the compounds disclosed in the present invention  
25 possess pharmacological activity only by virtue of an effect on a single biological process, it is believed that the compounds inhibit the effects of cytokines by virtue of inhibition of the enzyme p38 kinase. P38 kinase, otherwise known as cytokine suppressive binding protein (hereinafter CSBP) and reactivating kinase (hereinafter RK), is a member of the mitogen-activated protein (hereinafter MAP) kinase family of enzymes which is known to be activated  
30 by physiological stress such as that induced by ionising radiation, cytotoxic agents, and toxins, for example endotoxins such as bacterial lipopolysaccharide, and by a variety of agents

such as the cytokines, for example  $\text{TNF}\alpha$  and IL-1. It is known that p38 kinase phosphorylates certain intracellular proteins which are involved in the cascade of enzymatic steps which leads to the biosynthesis and excretion of cytokines such as  $\text{TNF}\alpha$  and IL-1.

Known inhibitors of p38 kinase have been reviewed by G J Hanson in Expert Opinions on  
 5 Therapeutic Patents, 1997, 7, 729-733. p38 kinase is known to exist in isoforms identified as p38 $\alpha$  and p38 $\beta$ .

The compounds disclosed in the present invention are inhibitors of the production of cytokines such as TNF, in particular of  $\text{TNF}\alpha$ , and various interleukins, in particular IL-1.

According to one aspect of the present invention there is provided a compound of the  
 10 Formula I



wherein  $\text{R}^3$  is (1-6C)alkyl or halogeno;

Q is aryl or heteroaryl which optionally bears 1, 2, 3 or 4 substituents selected from hydroxy.

15 halogeno, trifluoromethyl, cyano, mercapto, nitro, amino, carboxy, carbamoyl, formyl,  
 (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy,

(1-3C)alkylenedioxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl,

(1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl,

N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl,

20 (2-6C)alkanoyloxy, (1-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl,

N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, N-(1-6C)alkyl-

(1-6C)alkanesulphonylamino, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl,

(1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-

(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, carboxy-(1-6C)alkyl,

25 (1-6C)alkoxycarbonyl-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-

- (1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, halogeno-(2-6C)alkoxy, hydroxy-(2-6C)alkoxy, (1-6C)alkoxy-(2-6C)alkoxy, cyano-(1-6C)alkoxy, carboxy-(1-6C)alkoxy, (1-6C)alkoxycarbonyl-(1-6C)alkoxy, carbamoyl-(1-6C)alkoxy, N-(1-6C)alkylcarbamoyl-(1-6C)alkoxy, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkoxy,
- 5 amino-(2-6C)alkoxy, (1-6C)alkylamino-(2-6C)alkoxy, di-[(1-6C)alkyl]amino-(2-6C)alkoxy, halogeno-(2-6C)alkylamino, hydroxy-(2-6C)alkylamino, (1-6C)alkoxy-(2-6C)alkylamino, cyano-(1-6C)alkylamino, carboxy-(1-6C)alkylamino, (1-6C)alkoxycarbonyl-(1-6C)alkylamino, carbamoyl-(1-6C)alkylamino, N-(1-6C)alkylcarbamoyl-(1-6C)alkylamino, N,N-di-[(1-6C)alkyl]carbamoyl-
- 10 (1-6C)alkylamino, amino-(2-6C)alkylamino, (1-6C)alkylamino-(2-6C)alkylamino, di-[(1-6C)alkyl]amino-(2-6C)alkylamino, N-(1-6C)alkyl-halogeno-(1-6C)alkylamino, N-(1-6C)alkyl-hydroxy-(2-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkoxy-(2-6C)alkylamino, N-(1-6C)alkyl-cyano-(1-6C)alkylamino, N-(1-6C)alkyl-carboxy-(1-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkoxycarbonyl-(1-6C)alkylamino,
- 15 N-(1-6C)alkyl-carbamoyl-(1-6C)alkylamino, N-(1-6C)alkyl-N-(1-6C)alkylcarbamoyl-(1-6C)alkylamino, N-(1-6C)alkyl-N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkylamino, N-(1-6C)alkyl-amino-(2-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkylamino-(2-6C)alkylamino, N-(1-6C)alkyl-di-[(1-6C)alkyl]amino-(2-6C)alkylamino, halogeno-(2-6C)alkanoylamino, hydroxy-(2-6C)alkanoylamino,
- 20 (1-6C)alkoxy-(2-6C)alkanoylamino, cyano-(2-6C)alkanoylamino, carboxy-(2-6C)alkanoylamino, (1-6C)alkoxycarbonyl-(2-6C)alkanoylamino, carbamoyl-(2-6C)alkanoylamino, N-(1-6C)alkylcarbamoyl-(2-6C)alkanoylamino, N,N-di-[(1-6C)alkyl]carbamoyl-(2-6C)alkanoylamino, amino-(2-6C)alkanoylamino, (1-6C)alkylamino-(2-6C)alkanoylamino, di-[(1-6C)alkyl]amino-(2-6C)alkanoylamino, aryl, aryl-(1-6C)alkyl,
- 25 aryl-(1-6C)alkoxy, aryloxy, arylamino, N-(1-6C)alkyl-aryl-amino, aryl-(1-6C)alkylamino, N-(1-6C)alkyl-aryl-(1-6C)alkylamino, aroylamino, arylsulphonylamino, N-arylsulphamoyl, aryl-(2-6C)alkanoylamino, heteroaryl, heteroaryl-(1-6C)alkyl, heteroaryloxy, heteroaryl-(1-6C)alkoxy, heteroaryl-amino, N-(1-6C)alkyl-heteroaryl-amino, heteroaryl-(1-6C)alkylamino, N-(1-6C)alkyl-heteroaryl-(1-6C)alkylamino, heteroarylcarbonylamino,
- 30 heteroarylsulphonylamino,

- N-heteroarylsulphamoyl, heteroaryl-(2-6C)alkanoylamino, heterocyclyl, heterocyclyl-(1-6C)alkyl, heterocyclyloxy, heterocyclyl-(1-6C)alkoxy, heterocyclylamino, N-(1-6C)alkyl-heterocyclylamino, heterocyclyl-(1-6C)alkylamino, N-(1-6C)alkyl-heterocyclyl-(1-6C)alkylamino, heterocyclylcarbonylamino, heterocyclylsulphonylamino, 5 N-heterocyclylsulphamoyl and heterocyclyl-(2-6C)alkanoylamino, and wherein any aryl, heteroaryl or heterocyclyl group in a substituent on Q may optionally bear 1 or 2 substituents selected from hydroxy, halogeno, (1-6C)alkyl, (1-6C)alkoxy, carboxy, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, amino, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;
- 10 R<sup>2</sup> is hydroxy, halogeno, trifluoromethyl, cyano, mercapto, nitro, amino, carboxy, (1-6C)alkoxycarbonyl, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino or di-[(1-6C)alkyl]amino;
- p is 0, 1 or 2;
- q is 0, 1, 2, 3 or 4; and
- 15 R<sup>4</sup> is aryl, aryl-(1-6C)alkoxy, aryloxy, arylamino, N-(1-6C)alkyl-aryl-amino, aryl-(1-6C)alkylamino, N-(1-6C)alkyl-aryl-(1-6C)alkylamino, aroylamino, arylsulphonylamino, N-arylsulphamoyl, aryl-(2-6C)alkanoylamino, cycloalkyl, heteroaryl, heteroaryloxy, heteroaryl-(1-6C)alkoxy, heteroaryl-amino, N-(1-6C)alkyl-heteroaryl-amino, heteroaryl-(1-6C)alkylamino,
- 20 N-(1-6C)alkyl-heteroaryl-(1-6C)alkylamino, heteroarylcarbonylamino, heteroarylsulphonylamino, N-heteroarylsulphamoyl, heteroaryl-(2-6C)alkanoylamino, heterocyclyl, heterocyclyloxy, heterocyclyl-(1-6C)alkoxy, heterocyclylamino, N-(1-6C)alkyl-heterocyclylamino, heterocyclyl-(1-6C)alkylamino, N-(1-6C)alkyl-heterocyclyl-(1-6C)alkylamino, heterocyclylcarbonylamino,
- 25 heterocyclylsulphonylamino, N-heterocyclylsulphamoyl or heterocyclyl-(2-6C)alkanoylamino and R<sup>4</sup> optionally bears 1, 2, 3 or 4 substituents selected from hydroxy, halogeno, trifluoromethyl, cyano, mercapto, nitro, amino, carboxy, carbamoyl, formyl, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-3C)alkylenedioxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl,
- 30 (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl,

- (2-6C)alkanoyl, (2-6C)alkanoyloxy, (1-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-
- 5 (1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, carboxy-(1-6C)alkyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, halogeno-(2-6C)alkoxy, hydroxy-(2-6C)alkoxy, (1-6C)alkoxy-(2-6C)alkoxy, cyano-(1-6C)alkoxy, carboxy-(1-6C)alkoxy, (1-6C)alkoxycarbonyl-(1-6C)alkoxy, carbamoyl-(1-6C)alkoxy,
- 10 N-(1-6C)alkylcarbamoyl-(1-6C)alkoxy, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkoxy, amino-(2-6C)alkoxy, (1-6C)alkylamino-(2-6C)alkoxy, di-[(1-6C)alkyl]amino-(2-6C)alkoxy, halogeno-(2-6C)alkylamino, hydroxy-(2-6C)alkylamino, (1-6C)alkoxy-(2-6C)alkylamino, cyano-(1-6C)alkylamino, carboxy-(1-6C)alkylamino, (1-6C)alkoxycarbonyl-(1-6C)alkylamino, carbamoyl-(1-6C)alkylamino,
- 15 N-(1-6C)alkylcarbamoyl-(1-6C)alkylamino, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkylamino, amino-(2-6C)alkylamino, (1-6C)alkylamino-(2-6C)alkylamino, di-[(1-6C)alkyl]amino-(2-6C)alkylamino, N-(1-6C)alkyl-halogeno-(1-6C)alkylamino, N-(1-6C)alkyl-hydroxy-(2-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkoxy-(2-6C)alkylamino, N-(1-6C)alkyl-cyano-(1-6C)alkylamino, N-(1-6C)alkyl-
- 20 carboxy-(1-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkoxycarbonyl-(1-6C)alkylamino, N-(1-6C)alkyl-carbamoyl-(1-6C)alkylamino, N-(1-6C)alkyl-N-(1-6C)alkylcarbamoyl-(1-6C)alkylamino, N-(1-6C)alkyl-N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkylamino, N-(1-6C)alkyl-amino-(2-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkylamino-(2-6C)alkylamino, N-(1-6C)alkyl-di-[(1-6C)alkyl]amino-(2-6C)alkylamino,
- 25 halogeno-(2-6C)alkanoylamino, hydroxy-(2-6C)alkanoylamino, (1-6C)alkoxy-(2-6C)alkanoylamino, cyano-(2-6C)alkanoylamino, carboxy-(2-6C)alkanoylamino, (1-6C)alkoxycarbonyl-(2-6C)alkanoylamino, carbamoyl-(2-6C)alkanoylamino, N-(1-6C)alkylcarbamoyl-(2-6C)alkanoylamino, N,N-di-[(1-6C)alkyl]carbamoyl-(2-6C)alkanoylamino, amino-(2-6C)alkanoylamino,
- 30 (1-6C)alkylamino-(2-6C)alkanoylamino, di-[(1-6C)alkyl]amino-(2-6C)alkanoylamino, aryl, aryl-(1-6C)alkyl, aryl-(1-6C)alkoxy, aryloxy, arylamino, N-(1-6C)alkyl-aryl-amino,

- aryl-(1-6C)alkylamino, N-(1-6C)alkyl-aryl-(1-6C)alkylamino, aroylamino, arylsulphonylamino, N-arylsulphamoyl, aryl-(2-6C)alkanoylamino, heteroaryl, heteroaryl-(1-6C)alkyl, heteroaryloxy, heteroaryl-(1-6C)alkoxy, heteroarylamino, N-(1-6C)alkyl-heteroarylamino, heteroaryl-(1-6C)alkylamino, N-(1-6C)alkyl-heteroaryl-
- 5 (1-6C)alkylamino, heteroarylcarbonylamino, heteroarylsulphonylamino, N-heteroarylsulphamoyl, heteroaryl-(2-6C)alkanoylamino, heterocyclyl, heterocyclyl-(1-6C)alkyl, heterocyclyoxy, heterocyclyl-(1-6C)alkoxy, heterocyclylamino, N-(1-6C)alkyl-heterocyclylamino, heterocyclyl-(1-6C)alkylamino, N-(1-6C)alkyl-heterocyclyl-(1-6C)alkylamino, heterocyclylcarbonylamino, heterocyclylsulphonylamino,
- 10 N-heterocyclylsulphamoyl and heterocyclyl-(2-6C)alkanoylamino, and wherein any aryl, heteroaryl or heterocyclyl group in a substituent on R<sup>4</sup> may optionally bear 1 or 2 substituents selected from hydroxy, halogeno, (1-6C)alkyl, (1-6C)alkoxy, carboxy, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, amino, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;
- 15 or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only and references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only. An

20 analogous convention applies to other generic terms.

It is to be understood that, insofar as certain of the compounds of Formula I defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of inhibiting cytokines, in particular TNF. The synthesis

25 of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, inhibitory properties against TNF may be evaluated using the standard laboratory techniques referred to hereinafter.

Suitable values for the generic radicals referred to above include those set out below.

A suitable value for Q or R<sup>4</sup> or for a substituent on Q or R<sup>4</sup> when it is aryl or for the aryl group within a substituent on Q or R<sup>4</sup> is, for example, phenyl or naphthyl, preferably phenyl.

A suitable value for Q or R<sup>4</sup> or for a substituent on Q or R<sup>4</sup> when it is heteroaryl or for  
 5 the heteroaryl group within a substituent on Q or R<sup>4</sup> is, for example, an aromatic 5- or 6-membered monocyclic ring or a 9- or 10-membered bicyclic ring with up to five ring heteroatoms selected from oxygen, nitrogen and sulphur, for example furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl,  
 10 benzofuranyl, indolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolyl, quinoxalyl, cinnolyl or naphthyridinyl, preferably furyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzofuranyl, indolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, benzofurazanyl, quinolyl,  
 15 isoquinolyl, quinazolyl, quinoxalyl or naphthyridinyl, more preferably isoxazolyl, pyridyl, benzothiazolyl, quinolyl, quinazolyl, quinoxalyl or naphthyridinyl.

A suitable value for R<sup>4</sup> or for a substituent on Q or R<sup>4</sup> when it is heterocyclyl or for the heterocyclyl group within a substituent on Q or R<sup>4</sup> is, for example, a non-aromatic saturated or partially saturated 5 to 10 membered monocyclic or bicyclic ring with up to five heteroatoms  
 20 selected from oxygen, nitrogen and sulphur, for example pyrrolinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl or tetrahydropyrimidinyl, preferably pyrrolidin-1-yl, morpholino, piperidino or piperazin-1-yl.

Suitable values for various R<sup>3</sup> or R<sup>2</sup> groups, or for various substituents on Q or R<sup>4</sup> or  
 25 on an aryl, heteroaryl or heterocyclyl group in a substituent on Q or R<sup>4</sup> include:-

for halogeno:	fluoro, chloro, bromo and iodo;
for (1-6C)alkyl:	methyl, ethyl, propyl, isopropyl and <u>tert</u> -butyl;
for (2-6C)alkenyl:	vinyl and allyl;
for (2-6C)alkynyl:	ethynyl and 2-propynyl;
30 for (1-6C)alkoxy:	methoxy, ethoxy, propoxy, isopropoxy and butoxy;

- for (1-6C)alkoxycarbonyl: methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl;
- for N-(1-6C)alkylcarbamoyl: N-methylcarbamoyl, N-ethylcarbamoyl and N-propylcarbamoyl;
- 5 for N,N-di-[(1-6C)alkyl]carbamoyl: N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl and N,N-diethylcarbamoyl;
- for (2-6C)alkanoyl: acetyl and propionyl;
- for (1-6C)alkylamino: methylamino, ethylamino and propylamino;
- for di-[(1-6C)alkyl]amino: dimethylamino, diethylamino and N-ethyl-N-methylamino.
- 10 A suitable value for R<sup>4</sup> when it is cycloalkyl is, for example, a non-aromatic mono- or bicyclic 4- to 10-membered carbon ring such as cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1]heptyl and bicyclo[4.4.0]decyl, preferably cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.
- 15 Suitable values for R<sup>4</sup> and suitable values for a substituent on Q or R<sup>4</sup> include:-
- for aryl-(1-6C)alkyl: benzyl and 2-phenylethyl;
- for aryl-(1-6C)alkoxy: benzyloxy and 2-phenylethoxy;
- for aryloxy: phenoxy and 2-naphthyloxy;
- for arylamino: anilino;
- 20 for N-(1-6C)alkyl-aryl-amino: N-methylanilino and N-ethylanilino;
- for aryl-(1-6C)alkylamino: benzylamino and 2-phenethylamino;
- for N-(1-6C)alkyl-aryl-(1-6C)alkylamino: N-benzyl-N-methylamino;
- for aroylamino: benzamido and 2-naphthoylethylamino;
- arylsulphonylamino: benzenesulphonylamido;
- 25 for N-arylsulphamoyl: N-phenylsulphamoyl;
- for aryl-(2-6C)alkanoylamino: phenylacetamido and 3-phenylpropionamido;
- for heteroaryl-(1-6C)alkyl: heteroarylmethyl and 2-heteroarylethyl;
- for heteroaryl-(1-6C)alkoxy: heteroarylmethoxy and 2-heteroarylethoxy;
- for N-(1-6C)alkyl-heteroarylamino: N-methylheteroarylamino;
- 30 for heteroaryl-(1-6C)alkylamino: heteroarylmethylamino and 2-heteroarylethylamino;

	for <u>N</u> -(1-6C)alkyl-heteroaryl-	<u>N</u> -methylheteroarylmethylamino and
	(1-6C)alkylamino:	<u>N</u> -methyl-2-heteroarylethylamino;
	for heteroaryl-(2-6C)alkanoylamino:	heteroarylacetamido and
5		3-heteroarylpropionamido;
	for heterocyclyl-(1-6C)alkyl:	heterocyclylmethyl and 2-heterocyclylethyl;
	for heterocyclyl-(1-6C)alkoxy:	heterocyclylmethoxy and 2-heterocyclylethoxy;
	for <u>N</u> -(1-6C)alkyl-heterocyclylamino:	<u>N</u> -methylheterocyclylamino;
	for heterocyclyl-(1-6C)alkylamino:	heterocyclylmethylamino and
10		2-heterocyclylethylamino;
	for <u>N</u> -(1-6C)alkyl-heterocyclyl-	
	(1-6C)alkylamino:	<u>N</u> -methylheterocyclylmethylamino and
	for heterocyclyl-(2-6C)alkanoylamino:	<u>N</u> -methyl-2-heterocyclylethylamino;
15		heterocyclylacetamido and
	for (1-3C)alkylenedioxy:	3-heterocyclylpropionamido;
		methylenedioxy, ethylenedioxy and
		propylenedioxy;
	for (1-6C)alkylthio:	methylthio, ethylthio and propylthio;
	for (1-6C)alkylsulphinyl:	methylsulphinyl, ethylsulphinyl and
20		propylsulphinyl;
	for (1-6C)alkylsulphonyl:	methylsulphonyl, ethylsulphonyl and
		propylsulphonyl;
	for (2-6C)alkanoyloxy:	acetoxy and propionyloxy;
	for (1-6C)alkanoylamino:	formamido, acetamido and propionamido;
25	for <u>N</u> -(1-6C)alkylsulphamoyl:	<u>N</u> -methylsulphamoyl and <u>N</u> -ethylsulphamoyl;
	for <u>N,N</u> -di-[(1-6C)alkyl]sulphamoyl:	<u>N,N</u> -dimethylsulphamoyl;
	for (1-6C)alkanesulphonylamino:	methanesulphonylamino and
		ethanesulphonylamino;
	for <u>N</u> -(1-6C)alkyl-	
30	(1-6C)alkanesulphonylamino:	<u>N</u> -methylmethanesulphonylamino
		and <u>N</u> -methylethanesulphonylamino;

	for halogeno-(1-6C)alkyl:	fluoromethyl, chloromethyl, bromomethyl, difluoromethyl, dichloromethyl, dibromomethyl, 2-fluoroethyl, 2-chloroethyl and 2-bromoethyl;
	for hydroxy-(1-6C)alkyl:	hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl and 3-hydroxypropyl;
5	for (1-4C)alkoxy-(1-6C)alkyl:	methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl;
	for cyano-(1-6C)alkyl:	cyanomethyl, 2-cyanoethyl, 1-cyanoethyl and 3-cyanopropyl;
10	for amino-(1-6C)alkyl:	aminomethyl, 2-aminoethyl, 1-aminoethyl and 3-aminopropyl;
	for (1-6C)alkylamino-(1-6C)alkyl:	methylaminomethyl, ethylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl, 2-ethylaminoethyl and 3-methylaminopropyl;
15	for di-[(1-6C)alkyl]amino-(1-6C)alkyl:	dimethylaminomethyl, diethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl and 3-dimethylaminopropyl;
20	for carboxy-(1-6C)alkyl:	carboxymethyl, 1-carboxyethyl, 2-carboxyethyl and 3-carboxypropyl;
	for (1-6C)alkoxycarbonyl-(1-6C)alkyl:	methoxycarbonylmethyl, ethoxycarbonylmethyl, t-butoxycarbonylmethyl, 1-methoxycarbonylethyl, 1-ethoxycarbonylethyl, 2-methoxycarbonylethyl, 2-ethoxycarbonylethyl, 3-methoxycarbonylpropyl and 3-ethoxycarbonylpropyl;
25	for carbamoyl-(1-6C)alkyl:	carbamoylmethyl, 1-carbamoylethyl, 2-carbamoylethyl and 3-carbamoylpropyl;
30	for <u>N</u> -(1-6C)alkylcarbamoyl-(1-6C)alkyl:	<u>N</u> -methylcarbamoylmethyl, <u>N</u> -ethylcarbamoylmethyl,

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	<u>N</u> -propylcarbamoylmethyl,
	1-( <u>N</u> -methylcarbamoyl)ethyl,
	1-( <u>N</u> -ethylcarbamoyl)ethyl,
	2-( <u>N</u> -methylcarbamoyl)ethyl,
5	2-( <u>N</u> -ethylcarbamoyl)ethyl and
	3-( <u>N</u> -methylcarbamoyl)propyl;
	for <u>N,N</u> -di-[(1-6C)alkyl]carbamoyl-
	(1-6C)alkyl:
10	<u>N,N</u> -dimethylcarbamoylmethyl,
	<u>N</u> -ethyl- <u>N</u> -methylcarbamoylmethyl,
	<u>N,N</u> -diethylcarbamoylmethyl,
	1-( <u>N,N</u> -dimethylcarbamoyl)ethyl,
	1-( <u>N,N</u> -diethylcarbamoyl)ethyl,
	2-( <u>N,N</u> -dimethylcarbamoyl)ethyl,
	2-( <u>N,N</u> -diethylcarbamoyl)ethyl and
15	3-( <u>N,N</u> -dimethylcarbamoyl)propyl;
	for halogeno-(2-6C)alkoxy:
	2-chloroethoxy, 2-bromoethoxy and
	3-chloropropoxy;
	for hydroxy-(2-6C)alkoxy:
	2-hydroxyethoxy, 3-hydroxypropoxy,
	2-hydroxy-2-methylethoxy and
20	4-hydroxybutoxy;
	for (1-6C)alkoxy-(2-6C)alkoxy:
	2-methoxyethoxy, 2-ethoxyethoxy,
	3-methoxypropoxy, 2-methoxy-1-methylethoxy
	and 4-ethoxybutoxy;
	for cyano-(1-6C)alkoxy:
	cyanomethoxy, 2-cyanoethoxy and
25	3-cyanopropoxy;
	for carboxy-(1-6C)alkoxy:
	carboxymethoxy, 2-carboxyethoxy and
	3-carboxypropoxy;
	for (1-6C)alkoxycarbonyl-(1-6C)alkoxy:
	methoxycarbonylmethoxy,
	ethoxycarbonylmethoxy,
30	<u>tert</u> -butoxycarbonylmethoxy,
	2-methoxycarbonylethoxy and

	3-ethoxycarbonylpropoxy;
for carbamoyl-(1-6C)alkoxy:	carbamoylmethoxy and 2-carbamoylethoxy;
for <u>N</u> -(1-6C)alkylcarbamoyl-(1-6C)alkoxy:	<u>N</u> -methylcarbamoylmethoxy,
	2-( <u>N</u> -ethylcarbamoyl)ethoxy and
5	3-( <u>N</u> -methylcarbamoyl)propoxy;
for <u>N,N</u> -di-[(1-6C)alkyl]carbamoyl-	
(1-6C)alkoxy:	<u>N,N</u> -dimethylcarbamoylmethoxy,
	2-( <u>N,N</u> -dimethylcarbamoyl)ethoxy and
	3-( <u>N,N</u> -diethylcarbamoyl)propoxy;
10 for amino-(2-6C)alkoxy:	2-aminoethoxy, 3-aminopropoxy and
	4-aminobutoxy;
for (1-6C)alkylamino-(2-6C)alkoxy:	2-methylaminoethoxy,
	2-methylamino-1-methylethoxy and
	3-ethylaminopropoxy;
15 for di-[(1-6C)alkyl]amino-(2-6C)alkoxy:	2-dimethylaminoethoxy, 2-diethylaminoethoxy,
	2-dimethylamino-2-methylethoxy and
	3-dimethylaminopropoxy;
for halogeno-(2-6C)alkylamino:	2-fluoroethylamino, 2-chloroethylamino,
	2-bromoethylamino, 3-fluoropropylamino and
20	3-chloropropylamino;
for hydroxy-(2-6C)alkylamino:	2-hydroxyethylamino, 3-hydroxypropylamino
	and 4-hydroxybutylamino;
for (1-6C)alkoxy-(2-6C)alkylamino:	2-methoxyethylamino,
	2-ethoxyethylamino, 3-methoxypropylamino and
25	3-ethoxypropylamino;
for cyano-(1-6C)alkylamino:	cyanomethylamino, 2-cyanoethylamino and
	3-cyanopropylamino;
for carboxy-(1-6C)alkylamino:	carboxymethylamino, 2-carboxyethylamino and
	3-carboxypropylamino;
30 for (1-6C)alkoxycarbonyl-	
(1-6C)alkylamino:	methoxycarbonylmethylamino.

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- for carbamoyl-(1-6C)alkylamino:
- 5 for N-(1-6C)alkylcarbamoyl-  
(1-6C)alkylamino:
- for N,N-di-[(1-6C)alkyl]carbamoyl-  
10 (1-6C)alkylamino:
- for amino-(2-6C)alkylamino:  
for (1-6C)alkylamino-(2-6C)alkylamino:  
15
- 20 for di-[(1-6C)alkyl]amino-  
(2-6C)alkylamino:
- 25
- for N-(1-6C)alkyl-halogeno-  
(2-6C)alkylamino:  
30
- 2-(ethoxycarbonyl)ethylamino and  
3-(tert-butoxycarbonyl)propylamino;  
carbamoylmethylamino and  
2-carbamoylethylamino;
- N-methylcarbamoylmethylamino,  
N-ethylcarbamoylmethylamino and  
2-(N-methylcarbamoyl)ethylamino;
- N,N-dimethylcarbamoyl-methylamino,  
N,N-diethylcarbamoylmethylamino and  
2-(N,N-dimethylcarbamoyl)ethylamino;  
2-aminoethylamino and 3-aminopropylamino;  
2-methylaminoethylamino,  
2-ethylaminoethylamino,  
2-propylaminoethylamino,  
3-methylaminopropylamino,  
3-ethylaminopropylamino and  
4-methylaminobutylamino;
- 2-dimethylaminoethylamino,  
2-(N-ethyl-N-methylamino)ethylamino,  
2-diethylaminoethylamino,  
2-dipropylaminoethylamino,  
3-dimethylaminopropylamino,  
3-diethylaminopropylamino and  
4-dimethylaminobutylamino;
- N-(2-chloroethyl)-N-methylamino,  
N-(2-bromoethyl)-N-methylamino and  
N-(2-bromoethyl)-N-ethylamino;

for N-(1-6C)alkyl-hydroxy-  
(2-6C)-alkylamino:

N-(2-hydroxyethyl)-N-methylamino,  
N-(3-hydroxypropyl)-N-methylamino and  
N-ethyl-N-(2-hydroxyethyl)amino;

5 for N-(1-6C)alkyl-(1-6C)alkoxy-  
(2-6C)-alkylamino:

N-methyl-N-(2-methoxyethyl)amino,  
N-methyl-N-(3-methoxypropyl)amino and  
N-ethyl-N-(2-methoxyethyl)amino;

for N-(1-6C)alkyl-cyano-(1-6C)alkylamino: N-(cyanomethyl)-N-methylamino;

10 for N-(1-6C)alkyl-carboxy-  
(1-6C)alkylamino:

N-carboxymethyl-N-methylamino and  
N-(2-carboxyethyl)-N-methylamino;

for N-(1-6C)alkyl-(1-6C)alkoxycarbonyl-  
(1-6C)alkylamino:

N-methoxycarbonylmethyl-N-methylamino,  
N-(2-ethoxycarbonyl)ethyl)-N-ethylamino and  
N-(2-tert-butoxycarbonyl)ethyl)-N-methylamino;

15 for N-(1-6C)alkyl-carbamoyl-  
(1-6C)alkylamino;

N-carbamoylmethyl-N-methylamino and  
N-(2-carbamoyl)ethyl)-N-methylamino;

20 for N-(1-6C)alkyl-N-

(1-6C)alkylcarbamoyl-(1-6C)alkylamino: N-(N-methylcarbamoylmethyl)-N-methylamino,  
N-(N-ethylcarbamoylmethyl)-N-methylamino  
and

N-[2-(N-methylcarbamoyl)ethyl]-  
N-methylamino;

25

for N-(1-6C)alkyl-N,N-di-

[(1-6C)alkyl]carbamoyl-(1-6C)alkylamino: N-(N,N-dimethylcarbamoylmethyl)-  
N-methylamino and N-[2-(N,N-  
dimethylcarbamoyl)ethyl]-N-methylamino;

30 for N-(1-6C)alkyl-amino-(2-6C)alkylamino: N-(2-aminoethyl)-N-methylamino and  
N-(3-aminopropyl)-N-methylamino;

- for N-(1-6C)alkyl-(1-6C)alkylamino-  
(2-6C)alkylamino: N-(2-methylaminoethyl)-N-methylamino and  
N-(3-ethylaminopropyl)-N-ethylamino;
- for N-(1-6C)alkyl-di-[(1-6C)alkyl]amino-  
5 (2-6C)alkylamino: N-(2-dimethylaminoethyl)-N-methylamino,  
N-(2-diethylaminoethyl)-N-methylamino and  
N-(3-dimethylaminopropyl)-N-methylamino;
- for halogeno-(2-6C)alkanoylamino: 2-chloroacetamido and 3-chloropropionamido;
- for hydroxy-(2-6C)alkanoylamino: 2-hydroxyacetamido and  
10 3-hydroxypropionamido;
- for (1-6C)alkoxy-(2-6C)alkanoylamino: 2-methoxyacetamido and  
3-methoxypropionamido;
- for cyano-(2-6C)alkanoylamino: 2-cyanoacetamido and 3-cyanopropionamido;
- for carboxy-(2-6C)alkanoylamino: 2-carboxyacetamido and  
15 3-carboxypropionamido;
- for (1-6C)alkoxycarbonyl-(2-6C)alkanoyl: 2-methoxycarbonylacetamido,  
2-(tert-butoxycarbonyl)acetamido and  
3-methoxycarbonylpropionamido;
- for carbamoyl-(2-6C)alkanoylamino: 2-carbamoylacetamido,  
20 3-carbamoylpropionamido and  
4-carbamoylbutyramido;
- for N-(1-6C)alkylcarbamoyl-  
(2-6C)alkanoylamino: 2-(N-methylcarbamoyl)acetamido and  
3-(N-ethylcarbamoyl)propionamido;
- 25 for N,N-di-[(1-6C)alkyl]carbamoyl-  
(2-6C)alkanoylamino: 2-(N,N-dimethylcarbamoyl)acetamido,  
2-(N,N-diethylcarbamoyl)acetamido and  
3-(N,N-dimethylcarbamoyl)propionamido;
- for amino-(2-6C)alkanoylamino: 2-aminoacetamido, 2-aminopropionamido and  
30 3-aminopropionamido;

for (1-6C)alkylamino-(2-6C)alkanoylamino: 2-methylaminoacetamido,  
 2-ethylaminoacetamido,  
 2-methylaminopropionamido and  
 3-methylaminopropionamido;

5 for di-[(1-6C)alkyl]amino-

(2-6C)alkanoylamino: 2-dimethylaminoacetamido,  
 2-diethylaminoacetamido,  
 2-dimethylaminopropionamido and  
 3-dimethylaminopropionamido.

10 A suitable pharmaceutically-acceptable salt of a compound of the Formula I is, for example, an acid-addition salt of a compound of the Formula I which is sufficiently basic, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example a salt of a compound of the Formula I which is sufficiently acidic, for example an alkali or alkaline earth  
 15 metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Various forms of prodrugs are known in the art. For examples of such prodrug derivatives, see:

- 20 a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);  
 b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);  
 25 c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);  
 d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and  
 e) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

Examples of such pro-drugs may be used to form in-vivo-cleavable esters of a compound of the Formula I. An in-vivo-cleavable ester of a compound of the Formula I  
 30 containing a carboxy group is, for example, a pharmaceutically-acceptable ester which is cleaved in the human or animal body to produce the parent acid. Suitable pharmaceutically-

acceptable esters for carboxy include (1-6C)alkoxymethyl esters, for example methoxymethyl; (1-6C)alkanoyloxymethyl esters, for example pivaloyloxymethyl; phthalidyl esters; (3-8C)cycloalkoxycarbonyloxy(1-6C)alkyl esters, for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolan-2-ylmethyl esters, for example 5-methyl-  
 5 1,3-dioxolan-2-ylmethyl; and (1-6C)alkoxycarbonyloxyethyl esters, for example 1-methoxycarbonyloxyethyl; and may be formed at any carboxy group in the compounds of this invention.

Particular novel compounds of the invention include, for example, amide derivatives of the Formula I, or pharmaceutically-acceptable salts thereof, wherein:-

- 10 (a)  $R^3$  is (1-6C)alkyl such as methyl, ethyl, propyl and isopropyl, preferably methyl and ethyl, more preferably methyl; and Q,  $R^2$ ,  $R^4$ , p and q have any of the meanings defined hereinbefore or in this section relating to particular novel compounds of the invention;
- (b)  $R^3$  is halogeno such as fluoro, bromo and chloro, preferably chloro and bromo, more preferably chloro; and Q,  $R^2$ ,  $R^4$ , p and q have any of the meanings defined hereinbefore or in  
 15 this section relating to particular novel compounds of the invention;
- (c) Q is phenyl which bears 1, 2 or 3 substituents selected from hydroxy, halogeno, trifluoromethyl, cyano, nitro, amino, carboxy, (1-6C)alkyl, (1-6C)alkoxy, (1-3C)alkylenedioxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, (2-6C)alkanoyl, halogeno-(1-6C)alkyl, (1-6C)alkoxy-  
 20 (1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, halogeno-(2-6C)alkoxy, hydroxy-(2-6C)alkoxy, (1-6C)alkoxy-(2-6C)alkoxy, cyano-(1-6C)alkoxy, carboxy-(1-6C)alkoxy, (1-6C)alkoxycarbonyl-(1-6C)alkoxy, amino-(2-6C)alkoxy, (1-6C)alkylamino-(2-6C)alkoxy, di-[(1-6C)alkyl]amino-(2-6C)alkoxy, pyridyl-(1-6C)alkyl, imidazolyl-  
 25 (1-6C)alkyl, pyridyl-(1-6C)alkoxy, imidazolyl-(1-6C)alkoxy, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 4-(1-6C)alkylpiperazinyl, 4-(2-6C)alkanoylpiperazinyl, pyrrolidinyl-(1-6C)alkyl, piperidinyl-(1-6C)alkyl, morpholinyl-(1-6C)alkyl, piperazinyl-(1-6C)alkyl, 4-(1-6C)alkylpiperazinyl-(1-6C)alkyl, 4-(2-6C)alkanoylpiperazinyl-(1-6C)alkyl, pyrrolidinylloxy, piperidinylloxy,  
 30 1-(1-6C)alkylpiperidinylloxy, pyrrolidinyl-(2-6C)alkoxy, piperidinyl-(2-6C)alkoxy, morpholinyl-(2-6C)alkoxy, piperazinyl-(2-6C)alkoxy, 4-(1-6C)alkylpiperazinyl-

(2-6C)alkoxy and 4-(2-6C)alkanoylpiperazinyl-(2-6C)alkoxy; and  $R^2$ ,  $R^3$ ,  $R^4$ , p and q have any of the meanings defined hereinbefore or in this section relating to particular novel compounds of the invention;

(d) Q is a heteroaromatic 5- or 6-membered monocyclic ring or a 9- or  
 5 10-membered bicyclic ring with up to five ring heteroatoms selected from oxygen, nitrogen and sulphur which optionally bears 1 or 2 substituents selected from hydroxy, halogeno, trifluoromethyl, cyano, nitro, amino, carboxy, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino and (1-6C)alkoxycarbonyl; and  $R^2$ ,  $R^3$ ,  $R^4$ , p and q have any of the meanings defined hereinbefore or in this section relating to particular novel compounds of the  
 10 invention;

(e) Q is furyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzofuranyl, indolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl or naphthyridinyl which optionally bears 1 or 2  
 15 substituents selected from hydroxy, halogeno, trifluoromethyl, cyano, nitro, amino, carboxy, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino and (1-6C)alkoxycarbonyl; and  $R^2$ ,  $R^3$ ,  $R^4$ , p and q have any of the meanings defined hereinbefore or in this section relating to particular novel compounds of the invention;

20 (f) Q is 2- or 3-furyl, 2- or 3-thienyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-imidazolyl, 3- or 4-pyrazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 3- or 4-pyridazinyl, 2-, 4- or 5-pyrimidinyl, 2-pyrazinyl, 2-, 3-, 5- or 6-benzofuranyl, 2-, 3-, 5- or 6-indolyl, 2-, 3-, 5- or 6-benzothienyl, 2-, 5- or 6-benzoxazolyl, 2-, 5- or 6-benzimidazolyl, 2-, 5- or 6-benzothiazolyl,  
 25 3-, 5- or 6-indazolyl, 5-benzofurazanyl, 2-, 3-, 6- or 7-quinolyl, 3-, 6- or 7-isoquinolyl, 2-, 6- or 7-quinazolinyl, 2-, 6- or 7-quinoxalinyl, or 1,8-naphthyridin-2-yl or 1,8-naphthyridin-3-yl which optionally bears 1 or 2 substituents selected from hydroxy, halogeno, trifluoromethyl, cyano, nitro, amino, carboxy, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino and (1-6C)alkoxycarbonyl; and  $R^2$ ,  $R^3$ ,  $R^4$ , p and q  
 30 have any of the meanings defined hereinbefore or in this section relating to particular novel compounds of the invention;

- (g) q is 0, and R<sup>4</sup> is phenyl which bears 1, 2 or 3 substituents selected from hydroxy, halogeno, trifluoromethyl, cyano, amino, (1-6C)alkyl, (1-6C)alkoxy, (1-3C)alkylenedioxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyl, halogeno-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl,
- 5 di-[(1-6C)alkyl]amino-(1-6C)alkyl, halogeno-(2-6C)alkoxy, hydroxy-(2-6C)alkoxy, (1-6C)alkoxy-(2-6C)alkoxy, cyano-(2-6C)alkoxy, carboxy-(2-6C)alkoxy, (1-6C)alkoxycarbonyl-(1-6C)alkoxy, amino-(2-6C)alkoxy, (1-6C)alkylamino-(2-6C)alkoxy, di-[(1-6C)alkyl]amino-(2-6C)alkoxy, halogeno-(2-6C)alkylamino, hydroxy-(2-6C)alkylamino, (1-6C)alkoxy-(2-6C)alkylamino, amino-
- 10 (2-6C)alkylamino, (1-6C)alkylamino-(2-6C)alkylamino, di-[(1-6C)alkyl]amino-(2-6C)alkylamino, N-(1-6C)alkyl-halogeno-(2-6C)alkylamino, N-(1-6C)alkyl-hydroxy-(2-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkoxy-(2-6C)alkylamino, N-(1-6C)alkyl-amino-(2-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkylamino-(2-6C)alkylamino, N-(1-6C)alkyl-di-[(1-6C)alkyl]amino-(2-6C)alkylamino, phenyl, benzyl,
- 15 benzyloxy, pyridyl, imidazolyl, pyridyl-(1-6C)alkyl, imidazolyl-(1-6C)alkyl, pyridyl-(1-6C)alkoxy, imidazolyl-(1-6C)alkoxy, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 4-(1-6C)alkylpiperazinyl, 4-(2-6C)alkanoylpiperazinyl, pyrrolidinyl-(1-6C)alkyl, piperidinyl-(1-6C)alkyl, morpholinyl-(1-6C)alkyl, piperazinyl-(1-6C)alkyl, 4-(1-6C)alkylpiperazinyl-(1-6C)alkyl, 4-(2-6C)alkanoylpiperazinyl-(1-6C)alkyl, pyrrolidinyloxy, piperidinyloxy,
- 20 1-(1-6C)alkylpiperidinyloxy, pyrrolidinyl-(2-6C)alkoxy, piperidinyl-(2-6C)alkoxy, morpholinyl-(2-6C)alkoxy, piperazinyl-(2-6C)alkoxy, 4-(1-6C)alkylpiperazinyl-(2-6C)alkoxy and 4-(2-6C)alkanoylpiperazinyl-(2-6C)alkoxy; and R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, p and q have any of the meanings defined hereinbefore or in this section relating to particular novel compounds of the invention;
- 25 (h) p is 0; and Q, R<sup>3</sup>, R<sup>4</sup> and q have any of the meanings defined hereinbefore or in this section relating to particular novel compounds of the invention; and
- (i) q is 0, and R<sup>4</sup> is furyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzofuranyl, indolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, benzofurazanyl, quinolyl,
- 30 isoquinolyl, quinazolinyl, quinoxalinyl or naphthyridinyl which optionally bears 1 or 2 substituents selected from hydroxy, halogeno, trifluoromethyl, cyano, nitro, amino, carboxy,

(1-6C)alkyl, (1-6C)alkoxy,

(1-6C)alkylamino, di-[(1-6C)alkyl]amino and (1-6C)alkoxycarbonyl; and Q, R<sup>2</sup>, R<sup>3</sup> and p have any of the meanings defined hereinbefore or in this section relating to particular novel compounds of the invention;

5 (j) q is 0, and R<sup>4</sup> is 2- or 3-furyl, 2- or 3-thienyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-imidazolyl, 3- or 4-pyrazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 3- or 4-pyridazinyl, 2-, 4- or 5-pyrimidinyl, 2-pyrazinyl, 2-, 3-, 5- or 6-benzofuranyl, 2-, 3-, 5- or 6-indolyl, 2-, 3-, 5- or 6-benzothienyl, 2-, 5- or 6-benzoxazolyl, 2-, 5- or 6-benzimidazolyl,

10 2-, 5- or 6-benzothiazolyl, 3-, 5- or 6-indazolyl, 5-benzofurazanyl, 2-, 3-, 6- or 7-quinolyl, 3-, 6- or 7-isoquinolyl, 2-, 6- or 7-quinazolinyl, 2-, 6- or 7-quinoxaliny, or 1,8-naphthyridin-2-yl or 1,8-naphthyridin-3-yl which optionally bears 1 or 2 substituents selected from hydroxy, halogeno, trifluoromethyl, cyano, nitro, amino, carboxy, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylamino,

15 di-[(1-6C)alkyl]amino and (1-6C)alkoxycarbonyl; and Q, R<sup>2</sup>, R<sup>3</sup> and p have any of the meanings defined hereinbefore or in this section relating to particular novel compounds of the invention;

(k) q is 0, and R<sup>4</sup> is 4- or 5-oxazolyl, 4- or 5-isoxazolyl, 4- or 5-thiazolyl, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 5- or 6-benzofuranyl, 5- or 6-benzothienyl, 5- or

20 6-benzothiazolyl, 2-, 3-, 6- or 7-quinolyl, 2-, 6- or 7-quinazolinyl, 2-, 6- or 7-quinoxaliny, 1,8-naphthyridin-2-yl or 1,8-naphthyridin-3-yl which optionally bears 1, 2 or 3 substituents selected from hydroxy, fluoro, chloro, trifluoromethyl, cyano, methyl, ethyl, methoxy and ethoxy; and Q, R<sup>2</sup>, R<sup>3</sup> and p have any of the meanings defined hereinbefore or in this section relating to particular novel compounds of the invention; and

25 (l) q is 1, 2, 3 or 4, and R<sup>4</sup> is cycloalkyl; and Q, R<sup>2</sup>, R<sup>3</sup> and p have any of the meanings defined hereinbefore or in this section relating to particular novel compounds of the invention.

A preferred compound of the invention is an amide derivative of the Formula I wherein R<sup>3</sup> is methyl, ethyl, chloro or bromo;

Q is phenyl which bears 1, 2 or 3 substituents selected from hydroxy, fluoro, chloro, 30 trifluoromethyl, cyano, carboxy, methyl, ethyl, propyl, methoxy, ethoxy, methylenedioxy, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, acetyl, propionyl, chloromethyl,

- methoxymethyl, methylaminomethyl, ethylaminomethyl, dimethylaminomethyl, diethylaminomethyl, 2-chloroethoxy, 3-chloropropoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 2-methoxyethoxy, 2-ethoxyethoxy, 3-methoxypropoxy, 3-ethoxypropoxy, cyanomethoxy, carboxymethoxy, methoxycarbonylmethoxy, ethoxycarbonylmethoxy,
- 5 tert-butoxycarbonylmethoxy, 2-aminoethoxy, 3-aminopropoxy, 2-methylaminoethoxy, 2-ethylaminoethoxy, 3-methylaminopropoxy, 3-ethylaminopropoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-pyridylmethoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl,
- 10 4-methylpiperazin-1-yl, 4-acetylpiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, morpholinomethyl, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 4-acetylpiperazin-1-ylmethyl, piperidin-4-yloxy, 1-methylpiperidin-4-yloxy, 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy,
- 15 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-(4-acetylpiperazin-1-yl)ethoxy and 3-(4-acetylpiperazin-1-yl)propoxy, or Q is furyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzofuranyl, indolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl or
- 20 naphthyridinyl which optionally bears 1 or 2 substituents selected from hydroxy, fluoro, chloro, trifluoromethyl, cyano, methyl, ethyl, methoxy and ethoxy;
- p is 0;
- q is 0; and
- R<sup>4</sup> is phenyl which bears 1 or 2 substituents selected from hydroxy, fluoro, chloro,
- 25 trifluoromethyl, cyano, amino, methyl, ethyl, methoxy, ethoxy, methylenedioxy, methylamino, ethylamino, dimethylamino, diethylamino, acetyl, propionyl, chloromethyl, methoxymethyl, 2-methoxyethyl, methylaminomethyl, ethylaminomethyl, dimethylaminomethyl, diethylaminomethyl, 2-chloroethoxy, 3-chloropropoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 2-methoxyethoxy, 2-ethoxyethoxy, 3-methoxypropoxy,
- 30 3-ethoxypropoxy, cyanomethoxy, carboxymethoxy, methoxycarbonylmethoxy, ethoxycarbonylmethoxy, tert-butoxycarbonylmethoxy, 2-aminoethoxy, 3-aminopropoxy,

- 2-methylaminoethoxy, 2-ethylaminoethoxy, 3-methylaminopropoxy, 3-ethylaminopropoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-chloroethylamino, 2-hydroxyethylamino, 2-methoxyethylamino, 2-ethoxyethylamino, 2-aminoethylamino,
- 5 2-methylaminoethylamino, 2-ethylaminoethylamino, 2-dimethylaminoethylamino, 2-diethylaminoethylamino, N-(2-chloroethyl)-N-methylamino, N-(2-hydroxyethyl)-N-methylamino, N-(2-methoxyethyl)-N-methylamino, N-(2-ethoxyethyl)-N-methylamino, N-(2-aminoethyl)-N-methylamino, N-(2-methylaminoethyl)-N-methylamino, N-(2-dimethylaminoethyl)-N-methylamino, N-(3-aminopropyl)-
- 10 N-methylamino, N-(3-methylaminopropyl)-N-methylamino, N-(3-ethylaminopropyl)-N-methylamino, N-(3-dimethylaminopropyl)-N-methylamino, N-(3-diethylaminopropyl)-N-methylamino, phenyl, benzyl, benzyloxy, 2-pyridylmethoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-acetylpiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl,
- 15 morpholinomethyl, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 4-acetylpiperazin-1-ylmethyl, piperidin-4-yloxy, 1-methylpiperidin-4-yloxy, 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy,
- 20 3-(4-methylpiperazin-1-yl)propoxy, 2-(4-acetylpiperazin-1-yl)ethoxy and 3-(4-acetylpiperazin-1-yl)propoxy;
- or a pharmaceutically-acceptable salt thereof.

A further preferred compound of the invention is an amide derivative of the Formula I wherein R<sup>3</sup> is methyl or chloro;

- 25 Q is phenyl which bears 1, 2 or 3 substituents selected from hydroxy, fluoro, chloro, cyano, carboxy, methyl, ethyl, propyl, methoxy, ethoxy, methylenedioxy, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, acetyl, propionyl, chloromethyl, dimethylaminomethyl, diethylaminomethyl, 2-methoxyethoxy, 2-ethoxyethoxy, 3-methoxypropoxy, 3-ethoxypropoxy, methoxycarbonylmethoxy, ethoxycarbonylmethoxy, tert-
- 30 butoxycarbonylmethoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy,

- 2-pyridylmethoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-acetylpiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, morpholinomethyl, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 4-acetylpiperazin-1-ylmethyl,
- 5 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-(4-acetylpiperazin-1-yl)ethoxy and 3-(4-acetylpiperazin-1-yl)propoxy, or Q is 2-furyl, 2-thienyl, 2-oxazolyl, 3-isoxazolyl,
- 10 2-imidazolyl, 2-thiazolyl, 3-isothiazolyl, 2-, 3- or 4-pyridyl, 3-pyridazinyl, 2- or 4-pyrimidinyl, 2-pyrazinyl, 5- or 6-benzofuranyl, 5- or 6-indolyl, 5- or 6-benzothienyl, 5- or 6-benzoxazolyl, 5- or 6-benzimidazolyl, 5- or 6-benzothiazolyl, 5- or 6-indazolyl, 2-, 6- or 7-quinolyl, 6- or 7-isoquinolyl, 2-, 6- or 7-quinazolinyl, 2-, 6- or 7-quinoxalinyll or 1,8-naphthyridin-3-yl which optionally bears 1 or 2 substituents selected from hydroxy,
- 15 chloro, methyl and ethyl;
- p is 0;
- q is 0; and
- R<sup>4</sup> is phenyl which bears 1 or 2 substituents selected from hydroxy, fluoro, chloro, cyano, amino, methyl, methoxy, methylamino, dimethylamino, 2-chloroethoxy,
- 20 3-chloropropoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 2-methoxyethoxy, 3-methoxypropoxy, carboxymethoxy, methoxycarbonylmethoxy, ethoxycarbonylmethoxy, tert-butoxycarbonylmethoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-pyridylmethoxy, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-acetylpiperazin-1-yl,
- 25 pyrrolidin-1-ylmethyl, piperidinomethyl, morpholinomethyl, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 4-acetylpiperazin-1-ylmethyl, 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-(4-acetylpiperazin-
- 30 1-yl)ethoxy and 3-(4-acetylpiperazin-1-yl)propoxy;
- or a pharmaceutically-acceptable salt thereof.

A further preferred compound of the invention is an amide derivative of the Formula I wherein  $R^3$  is methyl or chloro;

Q is phenyl which bears 1, 2 or 3 substituents selected from hydroxy, fluoro, chloro, cyano, carboxy, methyl, ethyl, propyl, methoxy, ethoxy, methylenedioxy, methoxycarbonyl,

5 ethoxycarbonyl, tert-butoxycarbonyl, acetyl, propionyl, chloromethyl, dimethylaminomethyl, diethylaminomethyl, 2-methoxyethoxy, 2-ethoxyethoxy, 3-methoxypropoxy,

3-ethoxypropoxy, methoxycarbonylmethoxy, ethoxycarbonylmethoxy, tert-butoxycarbonylmethoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy,

3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-pyridylmethoxy, 2-(imidazol-

10 1-yl)ethoxy, 3-(imidazol-1-yl)propoxy, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-acetylpiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, morpholinomethyl, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 4-acetylpiperazin-1-ylmethyl, 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperazin-1-ylethoxy,

15 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-(4-acetylpiperazin-1-yl)ethoxy and 3-(4-acetylpiperazin-1-yl)propoxy;

p is 0;

q is 1 or 2; and

$R^4$  is cyclobutyl, cyclopentyl or cyclohexyl;

20 or a pharmaceutically-acceptable salt thereof.

A more preferred compound of the invention is an amide derivative of the Formula I wherein  $R^3$  is methyl or chloro;

Q is phenyl which bears 1, 2 or 3 substituents selected from hydroxy, cyano, carboxy, methyl, ethyl, propyl, methoxy, ethoxy, acetyl and 2-methoxyethoxy;

25 p is 0;

q is 0; and

$R^4$  is phenyl which bears 1 or 2 substituents selected from chloro, cyano and dimethylamino; or a pharmaceutically-acceptable salt thereof.

A further more preferred compound of the invention is an amide derivative of the  
30 Formula I wherein  $R^3$  is methyl or chloro;

Q is 3-isoxazolyl, 3-pyridyl or 6-quinolyl which optionally bears a substituent selected from chloro and methyl;

p is 0;

q is 0; and

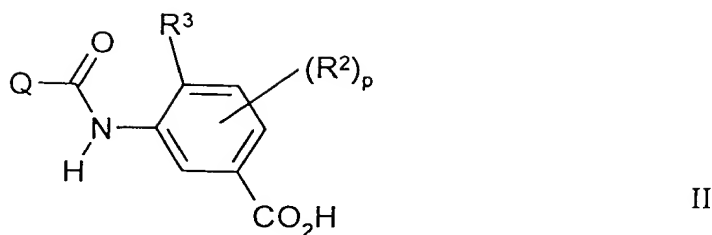
- 5 R<sup>4</sup> is phenyl which bears a dimethylamino substituent;  
or a pharmaceutically-acceptable salt thereof.

A particular preferred compound of the invention is, for example :-

- N-(3-dimethylaminophenyl)-4-methyl-3-(4-propylbenzamido)benzamide,  
3-(3,4-dimethoxybenzamido)-N-(3-dimethylaminophenyl)-4-methylbenzamide,  
10 3-(4-butoxybenzamido)-N-(3-dimethylaminophenyl)-4-methylbenzamide,  
4-chloro-N-(3-dimethylaminophenyl)-3-(4-propylbenzamido)benzamide,  
3-(4-carboxybenzamido)-N-(3-dimethylaminophenyl)-4-methylbenzamide,  
N-(3,4-dichlorobenzyl)-3-(3,4,5-trimethoxybenzamido)-4-methylbenzamide,  
N-(2-cyclohexylethyl)-3-(3,4-dimethoxybenzamido)-4-methylbenzamide,  
15 N-(3-dimethylaminophenyl)-4-methyl-3-(6-quinolylcarbonylamino)benzamide or  
4-chloro-N-(3-dimethylaminophenyl)-3-(6-quinolylcarbonylamino)benzamide;  
or a pharmaceutically-acceptable salt thereof.

- An amide derivative of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, may be prepared by any process known to be applicable to the  
20 preparation of chemically-related compounds. Such processes, when used to prepare a novel amide derivative of the Formula I are provided as a further feature of the invention and are illustrated by the following representative process variants in which, unless otherwise stated, Q, R<sup>2</sup>, R<sup>3</sup>, p, q and R<sup>4</sup> have any of the meanings defined hereinbefore. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of  
25 such starting materials is described in conjunction with the following representative process variants and within the accompanying Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

- (a) A compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-  
30 cleavable ester thereof, may be prepared by reacting a benzoic acid of the Formula II, or a reactive derivative thereof,



with an amine of the Formula III



under standard amide bond forming conditions, wherein variable groups are as defined  
 5 hereinbefore and wherein any functional group is protected if necessary, and:

- (i) removing any protecting groups; and
- (ii) optionally forming a pharmaceutically-acceptable salt or in-vivo-cleavable ester.

A suitable activated derivative of an acid of the Formula II is, for example, an acyl  
 10 halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid  
 chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed  
 by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester,  
 for example an ester formed by the reaction of the acid and a phenol such as  
 pentafluorophenol, an ester such as pentafluorophenyl trifluoroacetate or an alcohol such as  
 15 N-hydroxybenzotriazole; an acyl azide, for example an azide formed by the reaction of the  
 acid and an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide  
 formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the  
 product of the reaction of the acid and a carbodiimide such as dicyclohexylcarbodiimide.

The reaction is preferably carried out in the presence of a suitable base such as, for  
 20 example, an alkali or alkaline earth metal carbonate, alkoxide, hydroxide or hydride, for  
 example sodium carbonate, potassium carbonate, sodium ethoxide, potassium butoxide,  
 sodium hydroxide, potassium hydroxide, sodium hydride or potassium hydride, or an  
 organometallic base such as an alkyl-lithium, for example n-butyl-lithium, or a  
 dialkylamino-lithium, for example lithium di-isopropylamide, or, for example, an organic  
 25 amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine,  
 triethylamine, morpholine or diazabicyclo[5.4.0]undec-7-ene. The reaction is also preferably  
 carried out in a suitable inert solvent or diluent, for example tetrahydrofuran, methylene

chloride, 1,2-dimethoxyethane, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulphoxide or acetone, and at a temperature in the range, for example, -78 to 150°C, conveniently at or near ambient temperature.

Typically a carbodiimide coupling reagent is used in the presence of an organic solvent (preferably an anhydrous polar aprotic organic solvent) at a non-extreme temperature, for example in the region -10 to 40°C, typically at ambient temperature of about 20°C.

Protecting groups may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question and may be introduced by conventional methods. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower", as in, for example, lower alkyl, signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or arylaliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (for example isopropyl, tert-butyl); lower alkoxy lower alkyl groups (for example methoxymethyl, ethoxymethyl, isobutoxymethyl); lower aliphatic acyloxy lower alkyl groups, (for example acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl); lower alkoxycarbonyloxy lower alkyl groups (for example 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl); aryl lower alkyl groups (for example benzyl, p-methoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (for example trimethylsilyl and tert-butyldimethylsilyl); tri(lower alkyl)silyl lower alkyl groups (for example trimethylsilylethyl); and (2-6C)alkenyl groups (for example allyl and vinyllethyl). Methods

particularly appropriate for the removal of carboxyl protecting groups include for example acid-, base-, metal- or enzymically-catalysed hydrolysis.

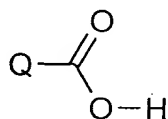
Examples of hydroxy protecting groups include lower alkyl groups (for example tert-butyl), lower alkenyl groups (for example allyl); lower alkanoyl groups (for example acetyl); lower alkoxy carbonyl groups (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl groups (for example allyloxycarbonyl); aryl lower alkoxy carbonyl groups (for example benzyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, *o*-nitrobenzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl); tri lower alkylsilyl (for example trimethylsilyl, tert-butyldimethylsilyl) and aryl lower alkyl (for example benzyl) groups.

10 Examples of amino protecting groups include formyl, aralkyl groups (for example benzyl and substituted benzyl, *p*-methoxybenzyl, nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-*p*-anisylmethyl and furylmethyl groups; lower alkoxy carbonyl (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl (for example allyloxycarbonyl); aryl lower alkoxy carbonyl groups (for example benzyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, 15 *o*-nitrobenzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl); trialkylsilyl (for example trimethylsilyl and tert-butyldimethylsilyl); alkylidene (for example methylenidene); benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base-, metal- or enzymically-catalysed hydrolysis for groups such as 20 *p*-nitrobenzyloxycarbonyl, hydrogenation for groups such as benzyl and photolytically for groups such as *o*-nitrobenzyloxycarbonyl.

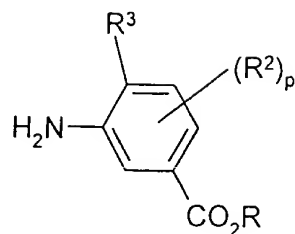
The reader is referred to Advanced Organic Chemistry, 4th Edition, by Jerry March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents. The reader is referred to Protective Groups in Organic Synthesis, 2nd Edition, by 25 Green *et al.*, published by John Wiley & Sons for general guidance on protecting groups.

The benzoic acid of Formula II may be prepared by the cleavage of the corresponding ester thereof which, in turn, may be prepared by reaction of an acid of Formula IV, or an activated derivative thereof as defined hereinbefore,



IV

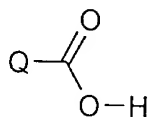
with an aniline of Formula V



V

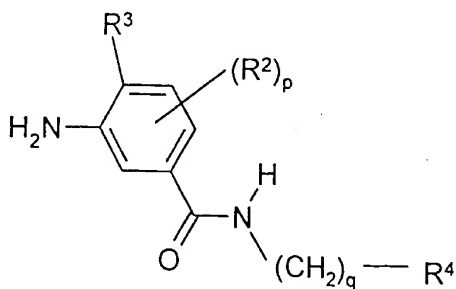
wherein R is, for example, lower alkyl or benzyl, under suitable amide bond forming conditions as defined hereinbefore.

- 5 Typical conditions include activating the carboxy group of the compound of Formula IV, for example by treatment with a halo reagent (for example oxalyl chloride) to form an acyl halide in an organic solvent at ambient temperature and then reacting the activated compound with the aniline of Formula V. Any functional groups are protected and deprotected as necessary.
- 10 (b) A compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, may be prepared by reacting an acid of the Formula IV, or an activated derivative thereof as defined hereinbefore,



IV

with an aniline of the Formula VI



VI

15 under standard amide bond forming conditions as defined hereinbefore, wherein variable groups are as defined hereinbefore and wherein any functional group is protected, if necessary, and:

- (i) removing any protecting groups;
- 20 (ii) optionally forming a pharmaceutically-acceptable salt or in-vivo-cleavable ester.

The aniline of Formula VII may be prepared by reduction of the corresponding nitro compound using convention procedures such as those illustrated in the Examples. Typical reaction conditions include the use of ammonium formate in the presence of a catalyst (for example palladium-on-carbon) in the presence of an organic solvent (preferably a polar protic solvent), preferably with heating, for example to about 60°C. Any functional groups are protected and deprotected as necessary.

(c) A compound of the Formula I wherein a substituent on Q or R<sup>4</sup> is (1-6C)alkoxy or substituted (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylamino, di-[(1-6C)alkyl]amino or substituted (1-6C)alkylamino, may be prepared by the alkylation, conveniently in the presence of a suitable base as defined hereinbefore, of an amide derivative of the Formula I wherein a substituent on Q or R<sup>4</sup> is hydroxy, mercapto or amino as appropriate.

The reaction is preferably carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulphoxide. The reaction is conveniently carried out at a temperature in the range, for example, 10 to 150°C, preferably in the range 20 to 80°C.

A suitable alkylating agent is, for example, any agent known in the art for the alkylation of hydroxy to alkoxy or substituted alkoxy, or for the alkylation of mercapto to alkylthio, or for the alkylation of amino to alkylamino or substituted alkylamino, for example an alkyl or substituted alkyl halide, for example a (1-6C)alkyl chloride, bromide or iodide or a substituted (1-6C)alkyl chloride, bromide or iodide, in the presence of a suitable base as defined hereinbefore, in a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 10 to 140°C, conveniently at or near ambient temperature.

(d) A compound of the Formula I wherein a substituent on Q or R<sup>4</sup> is (1-6C)alkanoylamino or substituted (2-6C)alkanoylamino may be prepared by the acylation of a compound of the Formula I wherein a substituent on Q or R<sup>4</sup> is amino.

A suitable acylating agent is, for example, any agent known in the art for the acylation

of amino to acylamino, for example an acyl halide, for example a (1-6C)alkanoyl chloride or bromide, conveniently in the presence of a suitable base, as defined hereinbefore, an alkanoic acid anhydride or mixed anhydride, for example a (1-6C)alkanoic acid anhydride such as acetic anhydride or the mixed anhydride formed by the reaction of an alkanoic acid and a  
 5 (1-6C)alkoxycarbonyl halide, for example a (1-6C)alkoxycarbonyl chloride, in the presence of a suitable base as defined hereinbefore. In general the acylation is carried out in a suitable inert solvent or diluent as defined hereinbefore and at a temperature, in the range, for example, -30 to 120°C, conveniently at or near ambient temperature.

(e) A compound of the Formula I wherein a substituent on Q or R<sup>4</sup> is

10 (1-6C)alkanesulphonylamino may be prepared by the reaction of a compound of the Formula I wherein a substituent on Q or R<sup>4</sup> is amino with a (1-6C)alkanesulphonic acid, or an activated derivative thereof.

A suitable activated derivative of a (1-6C)alkanesulphonic acid is, for example, an alkanesulphonyl halide, for example an alkanesulphonyl chloride formed by the reaction of  
 15 the sulphonic acid and an inorganic acid chloride, for example thionyl chloride. The reaction is preferably carried out in the presence of a suitable base as defined hereinbefore, particularly pyridine, and in a suitable inert solvent or diluent as defined hereinbefore, particularly methylene chloride.

(f) A compound of the Formula I wherein a substituent on Q or R<sup>4</sup> is carboxy, carboxy-  
 20 (1-6C)alkyl, carboxy-(1-6C)alkoxy, carboxy-(1-6C)alkylamino, N-(1-6C)alkyl-carboxy-(1-6C)alkylamino or carboxy-(2-6C)alkanoylamino may be prepared by the cleavage of a compound of the Formula I wherein a substituent on Q or R<sup>4</sup> is (1-6C)alkoxycarbonyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, (1-6C)alkoxycarbonyl-(1-6C)alkoxy, (1-6C)alkoxycarbonyl-(1-6C)alkylamino,  
 25 N-(1-6C)alkyl-(1-6C)alkoxycarbonyl-(1-6C)alkylamino or (1-6C)alkoxycarbonyl-(2-6C)alkanoylamino as appropriate.

The cleavage reaction may conveniently be carried out by any of the many procedures known in the art for such a transformation. The reaction may be carried out, for example, by hydrolysis under acidic or basic conditions. A suitable base is, for example, an alkali metal.  
 30 alkaline earth metal or ammonium carbonate or hydroxide, for example sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide or ammonium hydroxide. The

reaction is preferably carried out in the presence of water and a suitable solvent or diluent such as methanol or ethanol. The reaction is conveniently carried out at a temperature in the range 10 to 150°C, preferably at or near ambient temperature.

The following biological assays and Examples serve to illustrate the present invention.

## 5 Biological Assays

The following assays can be used to measure the p38 kinase-inhibitory, the TNF-inhibitory and anti-arthritis effects of the compounds of the present invention:

### In vitro enzyme assay

The ability of compounds of the invention to inhibit the enzyme p38 kinase was  
10 assessed. Activity of test compounds against each of the p38 $\alpha$  and p38 $\beta$  isoforms of the enzyme was determined.

Human recombinant MKK6 (GenBank Accession Number G1209672) was isolated from Image clone 45578 (Genomics, 1996, 33, 151) and utilised to produce protein in the form of a GST fusion protein in a pGEX vector using analogous procedures to those disclosed  
15 by J. Han *et al.*, Journal of Biological Chemistry, 1996, 271, 2886-2891. p38 $\alpha$  (GenBank Accession Number G529039) and p38 $\beta$  (GenBank Accession Number G1469305) were isolated by PCR amplification of human lymphoblastoid cDNA (GenBank Accession Number GM1416) and human foetal brain cDNA [synthesised from mRNA (Clontech, catalogue no. 6525-1) using a Gibco superscript cDNA synthesis kit] respectively using oligonucleotides  
20 designed for the 5' and 3' ends of the human p38 $\alpha$  and p38 $\beta$  genes using analogous procedures to those described by J. Han *et al.*, Biochimica et Biophysica Acta, 1995, 1265, 224-227 and Y. Jiang *et al.*, Journal of Biological Chemistry, 1996, 271, 17920-17926.

Both p38 protein isoforms were expressed in *e coli* in PET vectors. Human recombinant p38 $\alpha$  and p38 $\beta$  isoforms were produced as 5' c-myc, 6His tagged proteins. Both  
25 MKK6 and the p38 proteins were purified using standard protocols: the GST MKK6 was purified using a glutathione sepharose column and the p38 proteins were purified using nickel chelate columns.

The p38 enzymes were activated prior to use by incubation with MKK6 for 3 hours at 30°C. The unactivated coli-expressed MKK6 retained sufficient activity to fully  
30 activate both isoforms of p38. The activation incubate comprised p38 $\alpha$  (10 $\mu$ l of 10mg/ml) or p38 $\beta$  (10 $\mu$ l of 5mg/ml) together with MKK6 (10 $\mu$ l of 1mg/ml), 'Kinase buffer' [100 $\mu$ l;

pH 7.4 buffer comprising Tris (50mM), EGTA (0.1mM), sodium orthovanadate (0.1mM) and  $\beta$ -mercaptoethanol (0.1%) and MgATP (30 $\mu$ l of 50mM  $\text{Mg}(\text{OCOCH}_3)_2$  and 0.5mM ATP).

This produced enough activated p38 enzyme for 3 Microtiter plates.

Test compounds were solubilised in DMSO and 10 $\mu$ l of a 1:10 diluted sample in  
5 'Kinase Buffer' was added to a well in a Microtiter plate. For single dose testing, the compounds were tested at 10 $\mu$ M. 'Kinase Assay Mix' [30 $\mu$ l; comprising Myelin Basic Protein (Gibco BRL cat. no. 1322B-010; 1ml of a 3.33mg/ml solution in water), activated p38 enzyme (50 $\mu$ l) and 'Kinase Buffer' (2ml)] was then added followed by 'Labelled ATP' [10 $\mu$ l; comprising 50 $\mu$ M ATP, 0.1 $\mu$ Ci  $^{33}\text{P}$  ATP (Amersham International cat. no. BF1000) and  
10 50mM  $\text{Mg}(\text{OCOCH}_3)_2$ ]. The plates were incubated at room temperature with gentle agitation. Plates containing p38 $\alpha$  were incubated for 90min and plates containing p38 $\beta$  were incubated for 45min. Incubation was stopped by the addition of 50 $\mu$ l of 20% trichloroacetic acid (TCA). The precipitated protein was phosphorylated by p38 kinase and test compounds were assessed for their ability to inhibit this phosphorylation. The plates were filtered using a  
15 Canberra Packard Unifilter and washed with 2% TCA, dried overnight and counted on a Top Count scintillation counter.

Test compounds were tested initially at a single dose and active compounds were retested to allow  $\text{IC}_{50}$  values to be determined.

#### In vitro cell-based assays

##### 20 (i) PBMC

The ability of compounds of this invention to inhibit  $\text{TNF}\alpha$  production was assessed by using human peripheral blood mononuclear cells which synthesise and secrete  $\text{TNF}\alpha$  when stimulated with lipopolysaccharide.

Peripheral blood mononuclear cells (PBMC) were isolated from heparinised  
25 (10units/ml heparin) human blood by density centrifugation (Lymphoprep<sup>TM</sup>; Nycomed). Mononuclear cells were resuspended in culture medium [RPMI 1640 medium (Gibco) supplemented with 50 units/ml penicillin, 50 $\mu$ g/ml streptomycin, 2mM glutamine and 1% heat-inactivated human AB serum (Sigma H-1513)]. Compounds were solubilised in DMSO at a concentration of 50mM, diluted 1:100 in culture medium and subsequently serial  
30 dilutions were made in culture medium containing 1% DMSO. PBMCs ( $2.4 \times 10^5$  cells in 160 $\mu$ l culture medium) were incubated with 20 $\mu$ l of varying concentrations of test compound

(triplicate cultures) or 20µl culture medium containing 1% DMSO (control wells) for 30 minutes at 37°C in a humidified (5%CO<sub>2</sub>/95% air) incubator (Falcon 3072 ; 96 well flat-bottom tissue culture plates). 20µl lipopolysaccharide [LPS E.Coli 0111:B4 (Sigma L-4130), final concentration 10µg/ml] solubilised in culture medium was added to appropriate wells.

5 20µl culture medium was added to "medium alone" control wells. Six "LPS alone" and four "medium alone" controls were included on each 96 well plate. Varying concentrations of a known TNFα inhibitor were included in each test, i.e. an inhibitor of the PDE Type IV enzyme (for example see Semmler, J. Wachtel. H and Endres, S., Int. J. Immunopharmac. (1993), 15(3), 409-413) or an inhibitor of proTNFα convertase (for example, see McGeehan, 10 G. M. et al. Nature (1994) 370, 558-561). Plates were incubated for 7 hours at 37°C (humidified incubator) after which 100µl of the supernatant was removed from each well and stored at -70°C (96 well round-bottom plates; Corning 25850). TNFα levels were determined in each sample using a human TNFα ELISA (see WO92/10190 and Current Protocols in Molecular Biology, vol 2 by Frederick M. Ausbel et al., John Wiley and Sons Inc.).

15

% inhibition =

$$\frac{(\text{LPS alone} - \text{medium alone}) - (\text{test concentration} - \text{medium alone})}{(\text{LPS alone} - \text{medium alone})} \times 100$$

## 20 (ii) Human Whole Blood

The ability of the compounds of this invention to inhibit TNFα production was also assessed in a human whole blood assay. Human whole blood secretes TNFα when stimulated with LPS. This property of blood forms the basis of an assay which is used as a secondary test for compounds which profile as active in the PBMC test.

25 Heparinised (10 units/ml) human blood was obtained from volunteers. 160µl whole blood were added to 96 well round-bottom plates (Corning 25850). Compounds were solubilised and serially diluted in RPMI 1640 medium (Gibco) supplemented with 50 units/ml penicillin, 50µg/ml streptomycin and 2mM glutamine, as detailed above. 20µl of each test concentration was added to appropriate wells (triplicate cultures). 20µl of RPMI 1640 30 medium supplemented with antibiotics and glutamine was added to control wells. Plates were incubated for 30 minutes at 37°C (humidified incubator), prior to addition of 20µl LPS (final

concentration 10µg/ml). RPMI 1640 medium was added to control wells. Six "LPS alone" and four "medium alone" controls were included on each plate. A known TNFα synthesis/secretion inhibitor was included in each test. Plates were incubated for 6 hours at 37°C (humidified incubator). Plates were centrifuged (2000rpm for 10 minutes) and 100µl plasma removed and stored at -70°C (Corning 25850 plates). TNFα levels were measured by ELISA (see WO92/10190 and Current Protocols in Molecular Biology, vol 2 by Frederick M. Ausbel et al., John Wiley and Sons Inc.). The paired antibodies that were used in the ELISA were obtained from R&D Systems (catalogue nos. MAB610 anti-human TNFα coating antibody, BAF210 biotinylated anti-human TNFα detect antibody).

10

#### Ex vivo / In vivo assessment

The ability of the compounds of this invention as *ex vivo* TNFα inhibitors were assessed in the rat or mouse. Briefly, groups of male Wistar Alderley Park (AP) rats (180-210g) were dosed with compound (6 rats) or drug vehicle (10 rats) by the appropriate route, for example peroral (p.o.), intraperitoneal (i.p.) or subcutaneous (s.c.). Ninety minutes later rats were sacrificed using a rising concentration of CO<sub>2</sub> and bled out via the posterior vena cavae into 5 Units of sodium heparin/ml blood. Blood samples were immediately placed on ice and centrifuged at 2000 rpm for 10 min at 4°C and the harvested plasmas frozen at -20°C for subsequent assay of their effect on TNFα production by LPS-stimulated human blood.

The rat plasma samples were thawed and 175µl of each sample was added to a set format pattern in a 96 well round bottom plate (Corning 25850). 50µl of heparinized human blood was then added to each well, mixed and the plate was incubated for 30 min at 37°C (humidified incubator). LPS (25µl; final concentration 10µg/ml) was added to the wells and incubation continued for a further 5.5 hours. Control wells were incubated with 25µl of medium alone. Plates were then centrifuged for 10 min at 2000 rpm and 200µl of the supernatants were transferred to a 96 well plate and frozen at -20°C for subsequent analysis of TNF concentration by ELISA.

Data analysis by dedicated software calculates for each compound/dose:

$$\% \text{ inhibition} = \frac{\text{Mean TNF}\alpha \text{ (Controls)} - \text{Mean TNF}\alpha \text{ (Treated)}}{\text{Mean TNF}\alpha \text{ (Controls)}} \times 100$$

30 of TNFα

Alternatively, mice could be used instead of rats in the above procedure.

### Test as anti-arthritic agent

Activity of a compound as an anti-arthritic agent was tested as follows. Acid soluble native type II collagen was shown by Trentham et al. [1] to be arthritogenic in rats; it caused polyarthritis when administered in Freund's incomplete adjuvant. This is now known as collagen-induced arthritis (CIA) and similar conditions can be induced in mice and primates. Recent studies have shown that anti-TNF monoclonal antibodies [2] and TNF receptor-IgG fusion proteins [3] ameliorate established CIA indicating that TNF plays a key role in the pathophysiology of CIA. Moreover, the remarkable efficacy reported for anti-TNF monoclonal antibodies in recent rheumatoid arthritis clinical trials indicates that TNF plays a major role in this chronic inflammatory disease. Thus CIA in DBA/1 mice as described in references 2 and 3 is a tertiary model which can be used to demonstrate the anti-arthritic activity of a compound. Also see reference 4.

1. Trentham, D.E. et al., (1977) J. Exp. Med., 146, 857.
2. Williams, R.O. et al., (1992) Proc Natl Acad Sci, 89, 9784.
3. Williams, R.O. et al., (1995) Immunology, 84, 433.
4. Badger, M. B. et al., (1996) The Journal of Pharmacology and Experimental Therapeutics 279, 1453-1461.

Although the pharmacological properties of the compounds of the Formula I vary with structural change as expected, in general a compound of the Formula I gives over 30% inhibition of p38 $\alpha$  and/or p38 $\beta$  at concentrations up to 10 $\mu$ M and over 30% inhibition in the PBMC test at concentrations up to 50 $\mu$ M. No physiologically unacceptable toxicity was observed at the effective dose for compounds tested of the present invention.

By way of example, the compound N-(3-dimethylaminophenyl)-4-methyl-3-(4-propylbenzamido)benzamide [Example 3, Compound No. 1] has an IC<sub>50</sub> of approximately 0.3 $\mu$ M against p38 $\alpha$  and an IC<sub>50</sub> of approximately 6 $\mu$ M in the PBMC test; the compound N-(2-cyclohexylethyl)-3-(3,4-dimethoxybenzamido)-4-methylbenzamide [Example 11] has an IC<sub>50</sub> of approximately 1 $\mu$ M against p38 $\alpha$  and an IC<sub>50</sub> of approximately 8 $\mu$ M in the PBMC test and the compound N-(3-dimethylaminophenyl)-4-methyl-3-(6-quinolylcarbonylamino)benzamide [Example 12]

has an  $IC_{50}$  of approximately  $0.7\mu M$  against p38 $\alpha$  and an  $IC_{50}$  of approximately  $22\mu M$  in the PBMC test.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises an amide derivative of the Formula I, or a pharmaceutically-  
5 acceptable or in-vivo-cleavable ester thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible  
10 powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

15 The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

The amount of active ingredient that is combined with one or more excipients to  
20 produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

25 The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will  
30 generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be

administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however  
5 preferred, particularly in tablet form. Typically, unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention.

According to a further aspect of the invention there is provided an amide derivative of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, as defined hereinbefore for use in a method of treatment of the human or animal body by  
10 therapy.

According to a further aspect of the invention there is provided the use of an amide derivative of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment or medical conditions mediated by cytokines.

15 In a further aspect the present invention provides a method of treating diseases or medical conditions mediated by cytokines which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof.

In a further aspect the present invention provides the use of a compound of the  
20 Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, in the manufacture of a medicament for use in the treatment of diseases or medical conditions mediated by TNF, IL-1, IL-6 or IL-8.

In a further aspect the present invention provides a method of treating diseases or medical conditions mediated by TNF, IL-1, IL-6 or IL-8 which comprises administering to a  
25 warm-blooded animal an effective amount of a compound of the Formula I or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof.

In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof in the manufacture of a medicament for use in the treatment of diseases or medical conditions  
30 mediated by TNF.

In a further aspect the present invention provides a method of treating diseases or medical conditions mediated by TNF which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof.

5 In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, in the manufacture of a medicament for use in inhibiting TNF, IL-1, IL-6 or IL-8.

In a further aspect the present invention provides a method of inhibiting TNF, IL-1, IL-6 or IL-8 which comprises administering to a warm-blooded animal an effective amount  
10 of a compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof.

In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, in the manufacture of a medicament for use in inhibiting TNF.

15 In a further aspect the present invention provides a method of inhibiting TNF which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically-acceptable salt or in vivo-cleavable ester thereof.

In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, in the  
20 manufacture of a medicament for use in the treatment of diseases or medical conditions mediated by p38 kinase.

In a further aspect the present invention provides a method of treating diseases or medical conditions mediated by p38 kinase which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically-  
25 acceptable salt or in-vivo-cleavable ester thereof.

In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, in the manufacture of a medicament for use in the production of a p38 kinase inhibitory effect.

In a further aspect the present invention provides a method of providing a p38 kinase  
30 inhibitory effect which comprises administering to a warm-blooded animal an effective

amount of a compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof.

In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, in the  
5 manufacture of a medicament for use in the treatment of rheumatoid arthritis, asthma, irritable bowel disease, multiple sclerosis, AIDS, septic shock, ischaemic heart disease or psoriasis.

In a further aspect the present invention provides a method of treating rheumatoid arthritis, asthma, irritable bowel disease, multiple sclerosis, AIDS, septic shock, ischaemic heart disease or psoriasis which comprises administering to a warm-blooded animal an  
10 effective amount of a compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof.

The compounds of this invention may be used in combination with other drugs and therapies used in the treatment of disease states which would benefit from the inhibition of cytokines, in particular TNF and IL-1. For example, the compounds of the Formula I could  
15 be used in combination with drugs and therapies used in the treatment of rheumatoid arthritis, asthma, irritable bowel disease, multiple sclerosis, AIDS, septic shock, ischaemic heart disease, psoriasis and the other disease states mentioned earlier in this specification.

For example, by virtue of their ability to inhibit cytokines, the compounds of the Formula I are of value in the treatment of certain inflammatory and non-inflammatory  
20 diseases which are currently treated with a cyclooxygenase-inhibitory non-steroidal anti-inflammatory drug (NSAID) such as indomethacin, ketorolac, acetylsalicylic acid, ibuprofen, sulindac, tolmetin and piroxicam. Co-administration of a compound of the Formula I with a NSAID can result in a reduction of the quantity of the latter agent needed to produce a therapeutic effect. Thereby the likelihood of adverse side-effects from the NSAID  
25 such as gastrointestinal effects are reduced. Thus according to a further feature of the invention there is provided a pharmaceutical composition which comprises a compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, in conjunction or admixture with a cyclooxygenase inhibitory non-steroidal anti-inflammatory agent, and a pharmaceutically-acceptable diluent or carrier.

30 The compounds of the invention may also be used with anti-inflammatory agents such as an inhibitor of the enzyme 5-lipoxygenase.

The compounds of the Formula I may also be used in the treatment of conditions such as rheumatoid arthritis in combination with antiarthritic agents such as gold, methotrexate, steroids and penicillinamine, and in conditions such as osteoarthritis in combination with steroids.

5 The compounds of the present invention may also be administered in degradative diseases, for example osteoarthritis, with chondroprotective, anti-degradative and/or reparative agents such as Diacerhein, hyaluronic acid formulations such as Hyalan, Rumalon, Arteparon and glucosamine salts such as Anril.

The compounds of the Formula I may be used in the treatment of asthma in  
10 combination with antiasthmatic agents such as bronchodilators and leukotriene antagonists.

If formulated as a fixed dose such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically-active agent within its approved dosage range. Sequential use is contemplated when a combination formulation is inappropriate.

15 Although the compounds of the Formula I are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of cytokines. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

The invention will now be illustrated in the following non-limiting Examples in  
20 which, unless otherwise stated:-

(i) operations were carried out at ambient temperature, i.e. in the range 17 to 25°C and under an atmosphere of an inert gas such as argon unless otherwise stated;

(ii) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids by filtration;

25 (iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany or high pressure liquid chromatography (HPLC) was performed on C18 reverse phase silica, for example on a Dynamax C-18 60Å preparative reversed-phase column;

30 (iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) in general, the end-products of the Formula I have satisfactory microanalyses and their structures were confirmed by nuclear magnetic resonance (NMR) and/or mass spectral techniques; fast-atom bombardment (FAB) mass spectral data were obtained using a Platform spectrometer and, where appropriate, either positive ion data or negative ion data were  
5 collected; NMR chemical shift values were measured on the delta scale [proton magnetic resonance spectra were determined using a Varian Gemini 2000 spectrometer operating at a field strength of 300MHz or a Bruker AM250 spectrometer operating at a field strength of 250MHz]; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad;

10 (vi) intermediates were not generally fully characterised and purity was assessed by thin layer chromatographic, HPLC, infra-red (IR) and/or NMR analysis;

(vii) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus or an oil-bath apparatus; melting points for the end-products of the Formula I were determined after crystallisation from a conventional  
15 organic solvent such as ethanol, methanol, acetone, ether or hexane, alone or in admixture; and

(viii) the following abbreviations have been used:-

DMF	<u>N,N</u> -dimethylformamide
DMSO	dimethylsulphoxide

**Example 1** N-(3-dimethylaminophenyl)-3-(3-methoxybenzamido)-4-methylbenzamide

Triethylamine (0.101 g) was added to a stirred mixture of 3-amino-N-(3-dimethylaminophenyl)-4-methylbenzamide (0.135 g), 3-methoxybenzoyl chloride (0.13 g) and methylene chloride (5 ml) and the resultant mixture was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and a saturated aqueous sodium bicarbonate solution. The organic phase was evaporated and the residue was triturated under a mixture of ethyl acetate and isohexane. There was thus obtained the title compound as a solid (0.156 g); Mass Spectrum: 10  $M+H^+$  404.

The 3-amino-N-(3-dimethylaminophenyl)-4-methylbenzamide used as a starting material was prepared as follows :-

Oxalyl chloride (1.73 ml) and DMF (a few drops) were added in turn to a solution of 4-methyl-3-nitrobenzoic acid (3.0 g) in methylene chloride (30 ml) which had been cooled to 15  $0^{\circ}\text{C}$  and the resultant mixture was stirred at ambient temperature for 3 hours. The mixture was evaporated and the residue was dissolved in methylene chloride (30 ml).

3-Dimethylaminoaniline hydrochloride (2.89 g), 4-dimethylaminopyridine (0.169 g) and triethylamine (7.7 ml) were added in turn and the reaction mixture was stirred at ambient temperature for 16 hours. The reaction mixture was partitioned between methylene chloride 20 and a saturated aqueous sodium chloride solution. The organic phase was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained N-(3-dimethylaminophenyl)-4-methyl-3-nitrobenzamide as a yellow solid (3.75 g); NMR Spectrum: ( $\text{CDCl}_3$ ) 2.69 (s, 3H), 3.0 (s, 6H), 6.57 (d, 1H), 6.87 25 (d, 1H), 7.2 (m, 2H), 7.49 (d, 1H), 7.75 (broad s, 1H), 8.05 (d, 1H), 8.45 (s, 1H).

10% Palladium-on-carbon (0.369 g) was added to a solution of the material so obtained (3.69 g) in methanol (150 ml). Ammonium formate (7.8 g) was added and the resultant mixture was stirred and heated to reflux for 1.25 hours. The mixture was cooled to ambient temperature and filtered through diatomaceous earth. The filtrate was evaporated and 30 the residue was triturated under water. The resultant solid was dried under vacuum at  $55^{\circ}\text{C}$  to

give 3-amino-N-(3-dimethylaminophenyl)-

4-methylbenzamide as a white solid (3.04 g); NMR Spectrum: ( $\text{CDCl}_3$ ) 2.22 (s, 3H), 2.98 (s, 6H), 3.75 (broad s, 2H), 6.52 (m, 1H), 6.83 (d, 1H), 7.13 (s, 2H), 7.21 (m, 3H), 7.68 (broad s, 1H).

5

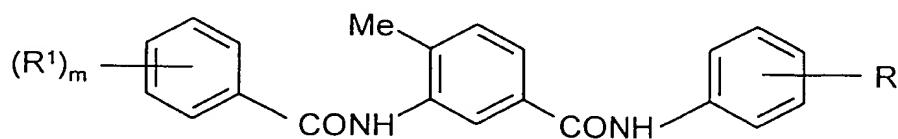
**Example 2** N-(3-dimethylaminophenyl)-4-methyl-3-(5-methylisoxazol-3-ylcarbonylamino)benzamide

Triethylamine (0.129 ml) was added to a stirred mixture of 3-amino-N-(3-dimethylaminophenyl)-4-methylbenzamide (0.1 g), 4-dimethylaminopyridine (5 mg), 5-methylisoxazol-3-ylcarbonyl chloride (0.081 g) and methylene chloride (3 ml) and the resultant mixture was stirred at ambient temperature for 16 hours. The mixture was diluted with methylene chloride (10 ml), washed with a saturated aqueous sodium bicarbonate solution and dried over magnesium sulphate. The organic solution was evaporated and the residue was triturated under isohexane. The resultant solid was dried at 55°C under vacuum to give the title compound as a solid (0.1 g); NMR Spectrum: ( $\text{CDCl}_3$ ) 2.42 (s, 3H), 2.55 (s, 3H), 2.97 (s, 6H), 6.55 (m, 2H), 6.89 (d, 1H), 7.23 (m, 2H), 7.36 (d, 1H), 7.72 (d, 1H), 7.84 (broad s, 1H), 8.55 (broad s, 2H); Mass Spectrum:  $\text{M}+\text{H}^+$  379.

**Example 3**

Using an analogous procedure to that described in Example 1 or 2, the appropriate benzoyl chloride (prepared by reaction of the corresponding benzoic acid with oxalyl chloride using an analogous procedure to that described in the first part of the portion of Example 1 which is concerned with the preparation of starting materials) was reacted with the appropriate aniline to give the compounds described in Table I.

Table I



No.	(R') <sub>m</sub>	R	Method	Note
1	4-propyl	3-dimethylamino	Ex. 2	(a)
2	4-ethyl	3-dimethylamino	Ex. 1	(b)
3	3,4-dimethyl	3-dimethylamino	Ex. 1	(c)
4	4-acetyl	3-dimethylamino	Ex. 2	(d)
5	4-methoxy	3-dimethylamino	Ex. 1	(e)
6	4-ethoxy	3-dimethylamino	Ex. 1	(f)
7	3,4-dimethoxy	3-dimethylamino	Ex. 2	(g)
8	3,4,5-trimethoxy	3-dimethylamino	Ex. 2	(h)
9	4-butoxy	3-dimethylamino	Ex. 1	(i)
10	3-cyano	3-dimethylamino	Ex. 1	(j)
11	3,4-methylenedioxy	3-dimethylamino	Ex. 1	(k)

### Notes

- 5 (a) The product gave the following data: NMR Spectrum: (CDCl<sub>3</sub>) 0.97 (t, 3H), 1.69 (m, 2H), 2.08 (s, 3H), 2.67 (t, 2H), 2.96 (s, 6H), 6.53 (d, 1H), 6.92 (d, 1H), 7.1 (d, 1H), 7.2 (t, 2H), 7.34 (d, 2H), 7.66 (m, 2H), 7.82 (d, 2H), 7.94 (broad s, 1H), 8.4 (broad s, 1H); Mass Spectrum: M+H<sup>+</sup> 416.
- (b) The product gave the following data: Mass Spectrum: M+H<sup>+</sup> 402.
- 10 (c) The product gave the following data: Mass Spectrum: M+H<sup>+</sup> 402.
- (d) The product gave the following data: NMR Spectrum: (CDCl<sub>3</sub>) 2.42 (s, 3H), 2.67 (s, 3H), 2.99 (s, 6H), 6.57 (d, 1H), 6.91 (d, 1H), 7.21 (m, 2H), 7.37 (d, 1H), 7.71 (d, 1H), 7.9 (m, 2H), 8.02 (d, 2H), 8.11 (d, 2H), 8.37 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 416. The 4-acetylbenzoyl chloride was prepared as follows :-
- 15 Oxalyl chloride (0.058 ml) was added to a solution of 4-acetylbenzoic acid (0.091 g) in a mixture of methylene chloride (3 ml) and DMF (a few drops) and the mixture was stirred at ambient temperature for 6 h. The mixture was evaporated to give the desired compound which was used without further purification.
- (e) The product gave the following data: Mass Spectrum: M+H<sup>+</sup> 404.

- (f) The product gave the following data: Mass Spectrum:  $M+H^+$  418.
- (g) The product gave the following data: NMR Spectrum: ( $DMSO-d_6$ ) 2.29 (s, 3H), 2.86 (s, 6H), 3.83 (s, 6H), 6.46 (d, 1H), 7.12 (m, 4H), 7.4 (d, 1H), 7.58 (broad s, 1H), 7.64 (d, 1H), 7.79 (d, 1H), 7.92 (s, 1H), 9.88 (s, 1H), 9.96 (s, 1H); Mass Spectrum:  $M+H^+$  434.
- 5 (h) The product was purified by column chromatography using increasingly polar mixtures of methylene chloride and methanol as eluent. The resultant product gave the following data: NMR Spectrum: ( $CDCl_3$ ) 2.24 (s, 3H), 2.93 (s, 6H), 3.89 (s, 9H), 6.5 (d, 1H), 6.92 (d, 1H), 7.15 (m, 5H), 7.54 (d, 1H), 7.84 (broad s, 1H), 8.11 (broad s, 1H), 8.32 (broad s, 1H); Mass Spectrum:  $M+H^+$  465.
- 10 (i) The product gave the following data: Mass Spectrum:  $M+H^+$  446.
- (j) The product gave the following data: Mass Spectrum:  $M+H^+$  399.
- (k) The product gave the following data: Mass Spectrum:  $M+H^+$  418.

**Example 4** N-(3-dimethylaminophenyl)-3-(4-hydroxybenzamido)-

15 **4-methylbenzamide**

Using an analogous procedure to that described in the last paragraph of the portion of Example 1 which is concerned with the preparation of starting materials, a mixture of 3-(4-benzyloxybenzamido)-N-(3-dimethylaminophenyl)-4-methylbenzamide (0.227 g), 10% palladium-on-carbon (0.028 g), ammonium formate (0.37 g) and methanol

20 (20 ml) was stirred and heated to reflux for 1.5 hours. The mixture was cooled to ambient temperature and filtered through diatomaceous earth. The filtrate was evaporated and the residue was triturated under water. The resultant solid was washed with a 100:1:0.12 mixture of methylene chloride, methanol and a saturated aqueous ammonium hydroxide solution and dried under vacuum at 55°C. There was thus obtained the title compound as a solid (0.104 g);

25 NMR Spectrum: ( $DMSO-d_6$ ) 2.26 (s, 3H), 2.84 (s, 6H), 6.44 (d, 1H), 6.84 (d, 2H), 7.13 (m, 3H), 7.39 (d, 1H), 7.76 (d, 1H), 7.86 (d, 2H), 7.92 (s, 1H), 9.73 (s, 1H), 9.91 (s, 1H); Mass Spectrum:  $M+H^+$  391.

The 3-(4-benzyloxybenzamido)-N-(3-dimethylaminophenyl)-4-methylbenzamide used as a starting material was prepared as follows :-

- 30 Oxalyl chloride (0.12 ml) was added to a solution of 4-benzyloxybenzoic acid (0.254 g) in a mixture of methylene chloride (5 ml) and DMF (a few drops) which had been cooled to

0°C. The resultant mixture was stirred at ambient temperature for 4 hours. The reaction mixture was evaporated and the residue was dissolved in methylene chloride (6 ml). 3-Amino-N-(3-dimethylaminophenyl)-4-methylbenzamide (0.3 g), 4-dimethylaminopyridine (0.014 g) and diisopropylethylamine (0.485 ml) were added in turn and the resultant solution  
5 was stirred at ambient temperature for 16 hours. The reaction mixture was partitioned between methylene chloride and a saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography using a 1:1 mixture of isohexane and ethyl acetate as eluent. There was thus obtained the required starting material as a solid (0.358 g); NMR Spectrum: (CDCl<sub>3</sub>) 2.39 (s, 3H), 2.98  
10 (s, 6H), 5.15 (s, 2H), 6.53 (d, 1H), 6.93 (d, 1H), 7.07 (d, 2H), 7.21 (m, 2H), 7.40 (m, 6H), 7.72 (m, 2H), 7.9 (m, 3H), 8.40 (s, 1H).

**Example 5**    N-(3-dimethylaminophenyl)-3-[4-(2-methoxyethoxy)benzamido]-4-methylbenzamide

15        2-Bromoethyl methyl ether (0.033 ml) was added to a stirred suspension of N-(3-dimethylaminophenyl)-3-(4-hydroxybenzamido)-4-methylbenzamide (0.90 g) and anhydrous potassium carbonate (0.064 g) in DMF (10 ml) and the resultant mixture was stirred at 80°C for 5 hours. The mixture was cooled to ambient temperature and partitioned between ethyl acetate and water. The organic phase was washed with a saturated aqueous  
20 sodium bicarbonate solution and with a saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated. The residue was triturated under diethyl ether. There was thus obtained the title compound as a solid (0.073 g); NMR Spectrum: (DMSO-d<sub>6</sub>) 2.28 (s, 3H), 2.87 (s, 6H), 3.31 (s, 3H), 3.67 (m, 2H), 4.18 (m, 2H), 6.43 (d, 1H) 7.12 (m, 5H), 7.37 (d, 1H), 7.78 (d, 1H), 7.97 (m, 3H), 9.87 (s, 1H), 9.96 (s, 1H); Mass Spectrum: M+H<sup>+</sup>  
25 448.

**Example 6**    4-chloro-N-(3-dimethylaminophenyl)-3-(4-propylbenzamido)-benzamide

Using an analogous procedure to that described in Example 1,  
30 4-chloro-3-(4-propylbenzamido)benzoyl chloride was reacted with 3-dimethylamino aniline dihydrochloride to give the title compound; NMR Spectrum: (DMSO-d<sub>6</sub>) 0.9 (t, 3H), 1.18 (t, 2H), 1.69 (m, 2H), 2.99 (s, 6H), 7.0 (d, 1H), 7.2-7.5 (m, 4H) 7.64-7.8 (m, 3H), 7.84

(d, 1H), 8.0 (m, 2H), 8.19 (s, 1H); Mass Spectrum:  $M+H^+$  436 and 438.

The 4-chloro-3-(4-propylbenzamido)benzoyl chloride used as starting material was prepared as follows:-

Acetyl chloride (1.67 ml) was added to a suspension of 3-amino-  
5 4-chlorobenzoic acid (2.0 g) in methanol (100 ml) and the mixture was stirred and heated to reflux for 16 hours. The mixture was allowed to cool and was evaporated. The residue was partitioned between methylene chloride and a saturated aqueous sodium bicarbonate solution. The organic phase was washed with a saturated aqueous sodium chloride solution and evaporated. There was thus obtained methyl 3-amino-  
10 4-chlorobenzoate as a solid (2.13 g) NMR Spectrum: ( $DMSO-d_6$ ) 3.79 (s, 3H), 5.62 (s, 2H), 7.06 (d, 1H), 7.29 (d, 1H), 7.4 (s, 2H).

Triethylamine (1.5 ml) was added to a stirred suspension of methyl 3-amino-4-chlorobenzoate (1.0 g) and 4-propylbenzoyl chloride (1.34 ml) in methylene chloride (50 ml) and the mixture was stirred at ambient temperature for 16 hours. The mixture was washed  
15 with a saturated aqueous sodium bicarbonate solution and evaporated. The residue was triturated under a mixture of ethyl acetate, diethyl ether and isohexane. There was thus obtained methyl 4-chloro-3-(4-propylbenzamido)-benzoate as a solid (1.05 g); NMR Spectrum: ( $DMSO-d_6$ ) 0.89 (t, 3H), 1.58-1.66 (m, 2H), 2.63 (t, 2H), 3.86 (s, 3H), 7.34 (d, 2H), 7.7 (d, 1H), 7.81 (d, 1H), 7.9 (d, 2H), 8.2 (s, 1H), 10.07 (s, 1H).

20 A 2N aqueous sodium hydroxide solution (3.02 ml) was added to a mixture of a portion (0.5 g) of the material so obtained, methanol (20 ml) and water (5 ml) and the resultant mixture was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was dissolved in water and extracted with ethyl acetate. The aqueous phase was acidified to pH2 and the resulting precipitate was isolated and washed  
25 with ethyl acetate and diethyl ether. There was thus obtained

4-chloro-3-(4-propylbenzamido)benzoic acid as a solid (0.175 g); NMR Spectrum: ( $DMSO-d_6$ ) 0.89 (t, 3H), 1.58-1.66 (m, 2H), 2.62 (t, 2H), 7.36 (d, 2H), 7.67 (d, 1H), 7.81 (d, 1H), 7.9 (d, 2H), 8.15 (s, 1H), 10.07 (s, 1H), 13.2 (broad s, 1H).

Oxalyl chloride (0.048 ml) was added dropwise to a stirred solution of a portion  
30 (0.16 g) of the material so obtained in a mixture of methylene chloride (20 ml) and DMF (a few drops) which had been cooled to 0°C. The mixture was allowed to warm to ambient

temperature and was stirred for 4 hours. The mixture was evaporated to give 4-chloro-3-(4-propylbenzamido)benzoyl chloride which was used without further purification.

**Example 7** 3-(4-carboxybenzamido)-N-(3-dimethylaminophenyl)-4-methyl-  
5 benzamide

A mixture of 3-(4-methoxycarbonylbenzamido)-N-(3-dimethylaminophenyl)-4-methylbenzamide (0.15 g), 2N aqueous sodium hydroxide solution (5 ml), methanol (2 ml) and THF (4 ml) was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was acidified with 2N aqueous hydrochloric acid. The resultant precipitate  
10 was isolated and dried under vacuum at 55°C to yield the title compound as a white solid (0.095 g); NMR Spectrum: (DMSO-d<sub>6</sub>) 2.32 (s, 3H), 3.06 (s, 6H), 7.28 (broad s, 1H), 7.43 (m, 2H), 7.7 (d, 1H), 7.84 (d, 1H), 8.0 (d, 2H), 8.1 (m, 4H), 10.26 (s, 1H), 10.46 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 418.

The 3-(4-methoxycarbonylbenzamido)-N-(3-dimethylaminophenyl)-4-  
15 methylbenzamide used as a starting material was obtained as follows :-

Triethylamine (0.26 ml) was added to a stirred mixture of 4-methoxycarbonylbenzoyl chloride (0.221 g), 4-dimethylaminopyridine (0.01 g), 3-amino-N-(3-dimethylaminophenyl)-4-methylbenzamide (0.2 g) and methylene chloride (10 ml) and the resultant mixture was stirred at ambient temperature for 16 hours. The  
20 mixture was diluted with methylene chloride and washed with a saturated aqueous sodium bicarbonate solution and with a saturated aqueous sodium chloride solution. The organic solution was dried over magnesium sulphate and evaporated. The residue was triturated under isohexane. The resultant solid was isolated and dried under vacuum at 55°C to give the required starting material as a solid (0.286 g); NMR Spectrum: (CDCl<sub>3</sub>) 2.4 (s, 3H), 2.98  
25 (s, 6H), 3.98 (s, 3H), 6.54 (m, 1H), 6.92 (d, 1H), 7.2 (m, 3H), 7.35 (d, 1H), 7.71 (d, 1H), 7.92 (s, 1H), 7.98 (d, 2H), 8.18 (d, 2H), 8.35 (s, 1H).

**Example 8** N-[2-(4-chlorophenoxy)ethyl]-3-(3,4-dimethoxybenzamido)-  
4-methylbenzamide

30 A solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.095 g) in methylene chloride (5 ml) was added to a stirred mixture of

3-(3,4-dimethoxybenzamido)-4-methylbenzoic acid (0.157 g), 2-(4-chlorophenoxy)-ethylamine (*C. Chim. Ther.*, 1973, 8, 259; 0.086 g), 4-dimethylaminopyridine (0.007 g), 1-hydroxybenzotriazole (0.074 g) and methylene chloride (5 ml). The resultant mixture was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and a saturated aqueous sodium bicarbonate solution. The organic phase was washed with an aqueous citric acid solution, dried over magnesium sulphate and evaporated. There was thus obtained the title compound as a solid (0.158 g); Mass Spectrum:  $M+H^+$  469.

The 3-(3,4-dimethoxybenzamido)-4-methylbenzoic acid used as a starting material was obtained as follows :-

Oxalyl chloride (10.5 ml) was added to a solution of 3,4-dimethoxybenzoic acid (18.2 g) in a mixture of methylene chloride (250 ml) and DMF (0.5 ml) which had been cooled to 0°C. The reaction mixture was allowed to warm to ambient temperature and was stirred for 4.5 hours. The mixture was evaporated and the residue was dissolved in methylene chloride (250 ml) and cooled to 0°C. Methyl 3-amino-4-methylbenzoate (11.0 g), 4-dimethylaminopyridine (0.81 g) and triethylamine (23.2 ml) were added and the reaction mixture was stirred at ambient temperature for 65 hours. The reaction mixture was washed in turn with 2N aqueous hydrochloric acid and with a saturated aqueous solution of sodium bicarbonate, dried over magnesium sulfate, and evaporated. There was thus obtained methyl 3-(3,4-dimethoxybenzamido)-4-methylbenzoate as a solid (28.6 g); NMR Spectrum: ( $CDCl_3$ ) 2.4 (s, 3H), 3.85 (m, 6H), 3.96 (s, 3H), 6.76 (d, 1H), 7.2-8.5 (m, 6H).

A solution of the material so obtained in a mixture of 2N aqueous sodium hydroxide solution (300 ml) and methanol (200 ml) was stirred at ambient temperature for 16 hours. The mixture was evaporated and the reaction mixture was partitioned between isohexane and water. The aqueous layer was acidified with aqueous hydrochloric acid and the resultant precipitate was isolated and dried under vacuum at 55°C to give 3-(3,4-dimethoxybenzamido)-4-methylbenzoic acid as a solid (25.05 g); NMR Spectrum: ( $DMSO-d_6$ ) 2.28 (s, 3H), 3.8 (m, 6H), 7.0-7.8 (m, 6H), 7.89 (s, 1H), 9.95 (s, 1H).

**Example 9** N-cyclobutyl-3-(3,4-dimethoxybenzamido)-4-methylbenzamide

Using an analogous procedure to that described in Example 8,

3-(3,4-dimethoxybenzamido)-4-methylbenzoic acid was reacted with cyclobutylamine to give the title compound; Mass Spectrum:  $M+H^+$  369.

5

**Example 10** N-(3,4-dichlorobenzyl)-3-(3,4,5-trimethoxybenzamido)-4-methylbenzamide

Using an analogous procedure to that described in Example 2,

3,4,5-trimethoxybenzoyl chloride was reacted with 3-amino-N-(3,4-dichlorobenzyl)-4-methylbenzamide to give the title compound which was purified by column chromatography using increasingly polar mixtures of methylene chloride and methanol as eluent; NMR Spectrum: ( $CDCl_3$ ) 2.28 (s, 3H), 3.87 (m, 9H), 4.48 (d, 2H), 7.13 (m, 5H), 7.36 (m, 2H), 7.52 (d, 1H), 8.01 (s, 1H), 8.13 (s, 1H); Mass Spectrum:  $M-H^+$  503.

15 The 3-amino-N-(3,4-dichlorobenzyl)-4-methylbenzamide used as a starting material was obtained as follows :-

Oxalyl chloride (4.8 ml) was added to a solution of 3-nitro-4-methylbenzoic acid (9.06 g) in methylene chloride (100 ml) and DMF (a few drops) and the reaction stirred at ambient temperature for 16 hours. The reaction mixture was evaporated and the residue was dissolved in methylene chloride (100 ml). 3,4-Dichlorobenzylamine (7.04 g), 4-dimethylaminopyridine (0.31 g) and triethylamine (13.9 ml) were added and the reaction mixture was stirred at ambient temperature for 16 hours. The mixture was washed with a saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography using a 250:8:1 mixture of methylene chloride, methanol and a saturated aqueous ammonium chloride solution as eluent to give

25 N-(3,4-dichlorobenzyl)-4-methyl-3-nitrobenzamide as a solid (9.95 g); NMR Spectrum: ( $DMSO-d_6$ ) 2.57 (s, 3H), 4.47 (d, 2H), 7.31 (m, 1H), 7.56 (m, 2H), 7.61 (d, 1H), 8.1 (m, 1H), 8.47 (d, 1H), 9.3 (t, 1H).

A solution of stannous chloride dihydrate (17.5 g) in concentrated hydrochloric acid (40 ml) was added to a solution of N-(3,4-dichlorobenzyl)-4-methyl-3-nitrobenzamide (5.85 g) in ethanol (40 ml) and concentrated hydrochloric acid

30

(40 ml). The reaction mixture was stirred and heated to reflux for 4 hours. The mixture was cooled and diluted with 2N aqueous hydrochloric acid. The reaction mixture was extracted several times with ethyl acetate, and the combined organic extracts were washed with a saturated solution of sodium bicarbonate, dried over magnesium sulphate and evaporated to give the required starting material as a solid (3.9 g); NMR Spectrum: ( $\text{CDCl}_3$ ) 2.2 (s, 3H), 3.74 (broad s, 2H), 4.58 (d, 2H), 6.4 (broad s, 1H), 7.02 (d, 1H), 7.1 (d, 1H), 7.19 (m, 2H), 7.42 (m, 2H).

**Example 11** N-(2-cyclohexylethyl)-3-(3,4-dimethoxybenzamido)-

10 4-methylbenzamide

Ammonium formate (0.224 g) was added to a stirred mixture of 10% palladium-on-carbon (0.015 g), N-(2-cyclohexen-1-ylethyl)-3-(3,4-dimethoxybenzamido)-4-methylbenzamide (0.15 g) and methanol (15 ml). and the reaction mixture was heated to reflux for 1.25 hours. The reaction mixture was allowed to cool and was filtered through diatomaceous earth. The filtrate was evaporated and the residue was triturated under water. The solid so obtained was dried under vacuum at 55°C to give the title compound as a powder (0.136 g); NMR Spectrum: ( $\text{CDCl}_3$ ) 0.8-2.3 (m, 13H), 2.37 (s, 3H), 3.45 (m, 2H), 3.96 (m, 6H), 6.12 (m, 1H), 6.93 (d, 1H), 7.26 (m, 1H), 7.46 (d, 1H), 7.56 (m, 2H), 7.92 (s, 1H), 8.16 (s, 1H); Mass Spectrum:  $\text{M}+\text{H}^+$  425.

20 The N-(2-cyclohexen-1-ylethyl)-3-(3,4-dimethoxybenzamido)-4-methylbenzamide used as a starting material was obtained as follows :-

2-Cyclohexen-1-ylethylamine (0.146 ml) was added to a stirred mixture of 3-(3,4-dimethoxybenzamido)-4-methylbenzoic acid (0.3 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.274 g), 4-dimethylaminopyridine (0.012 g) and methylene chloride (5 ml) and the reaction mixture was stirred at ambient temperature for 16 hours. The mixture was partitioned between methylene chloride and 2N aqueous hydrochloric acid. The organic phase was washed with a saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate and evaporated. There was thus obtained the required starting material as a solid (0.28 g); NMR Spectrum: ( $\text{CDCl}_3$ ) 1.6 (m, 4H), 2.0 (m, 4H), 2.23 (m, 2H), 2.37 (s, 3H), 3.51 (m, 2H), 3.96 (m, 6H), 5.54 (bs, 1H), 6.21 (broad s, 1H), 6.94 (d, 1H), 7.21 (m, 1H), 7.43 (m, 1H), 7.55

(m, 2H), 7.81 (broad s, 1H), 8.2 (broad s, 1H).

**Example 12** N-(3-dimethylaminophenyl)-4-methyl-3-(6-quinolylcarbonylamino)benzamide

- 5 Using an analogous procedure to that described in Example 2, 6-quinolylcarbonyl chloride was reacted with 3-amino-N-(3-dimethylaminophenyl)-4-methylbenzamide to give the title compound; NMR Spectrum: (DMSO<sub>d</sub><sub>6</sub>) 2.35 (s, 3H), 2.91 (s, 6H), 6.58 (m, 1H), 7.2 (m, 2H), 7.43 (d, 1H), 7.65 (m, 1H), 7.82 (d, 1H), 8.01 (s, 1H), 8.17 (m, 2H), 8.32 (d, 1H), 8.59 (d, 1H), 8.7 (d, 1H), 9.02 (s, 1H), 10.05 (s, 1H), 10.32 (s, 1H);
- 10 Mass Spectrum: M+H<sup>+</sup> 425.

The 6-quinolylcarbonyl chloride used as a starting material was prepared as follows :-

- Oxalyl chloride (0.058 ml) was added to a solution of 6-quinolinecarboxylic acid (0.096 g) in a mixture of methylene chloride (4 ml) and DMF (a few drops) and the reaction mixture was stirred at ambient temperature for 6 hours. The mixture was evaporated to give
- 15 the required starting material which was used without further purification.

**Example 13** 4-chloro-N-(3-dimethylaminophenyl)-3-(6-quinolylcarbonylamino)benzamide

- Using an analogous procedure to that described in Example 1,
- 20 4-chloro-3-(6-quinolylcarbonylamino)benzoyl chloride was reacted with 3-dimethylamino aniline dihydrochloride to give the title compound; NMR Spectrum: (DMSO<sub>d</sub><sub>6</sub>) 3.04 (s, 6H), 6.5 (d, 1H), 7.08-7.20(m, 3H), 7.61-7.64 (m, 1H), 7.74 (d, 1H), 7.92 (d, 1H) 8.1-8.2 (m, 2H), 7.31 (d, 1H), 8.58 (d, 1H), 8.72 (s, 1H), 9.02 (s, 1H) 10.13 (s, 1H), 10.5 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 445 and 447.

- 25 The 4-chloro-3-(6-quinolylcarbonylamino)benzoyl chloride used as starting material was prepared as follows:-

- Triethylamine (4.18 ml) was added to a stirred suspension of methyl (3-amino-4-chloro)benzoate (1.85 g) and 6-quinolylcarbonyl chloride (2.88 g) in methylene chloride (80 ml) and the resultant mixture was stirred at ambient temperature for 16 hours. The
- 30 mixture was washed with a saturated aqueous sodium bicarbonate solution, dried over

magnesium sulphate and evaporated. The residue was triturated under a mixture of ethyl acetate and diethyl ether. There was thus obtained methyl

4-chloro-3-(6-quinolylcarbonylamino)benzoate as a solid (1.1 g); NMR Spectrum: (DMSO<sub>d</sub><sub>6</sub>) 3.87 (s, 3H), 7.62-7.65 (m, 1H), 7.4 (d, 1H), 7.85 (d, 1H), 8.14 (d, 1H), 8.23-8.32 (m, 2H), 5 8.54 (d, 1H) 8.68 (s, 1H) 9.01 (s, 1H), 10.5 (s, 1H).

A 2N aqueous sodium hydroxide solution (2.21 ml) was added to a portion (0.5 g) of the material so obtained in a mixture of methanol (20 ml) and water (5 ml) and the resultant mixture was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was dissolved in water and extracted with ethyl acetate. The aqueous phase was 10 acidified to pH2 by the addition of dilute hydrochloric acid solution. The resultant precipitate was isolated and washed with diethyl ether. There was thus obtained 4-chloro-3-(6-quinolylcarbonylamino)benzoic acid hydrochloride salt as a solid (0.329 g); NMR Spectrum: (DMSO<sub>d</sub><sub>6</sub>) 7.64-7.68 (m, 1H), 7.7 (d, 1H), 7.83 (d, 1H), 8.14-8.19 (m, 2H), 8.29 (d, 1H), 8.57 (d, 1H) 8.7 (s, 1H) 9.03 (s, 1H).

15 Oxalyl chloride (0.048 ml) was added dropwise to a stirred solution of a portion (0.181 g) of the acid so obtained in a mixture of methylene chloride (20 ml) and DMF (a few drops) which had been cooled to 0°C. The mixture was allowed to warm to ambient temperature and was stirred for 4 hours. The solvent was evaporated to give 4-chloro-3-(6-quinolylcarbonylamino)benzoyl chloride which was used without further purification.

20

**Example 14 3-(6-chloropyrid-3-ylcarbonylamino)-N-(3-dimethylaminophenyl)-4-methylbenzamide**

Using an analogous procedure to that described in Example 1, 6-chloropyrid-3-ylcarbonyl chloride was reacted with 3-amino- 25 N-(3-dimethylaminophenyl)-4-methylbenzamide to give the title compound; Mass Spectrum: M+H<sup>+</sup> 409 and 411.

**Example 15 N-(3-dimethylaminophenyl)-4-methyl-3-(2-naphthoylamino)-benzamide**

Using an analogous procedure to that described in Example 1, 30 2-naphthoyl chloride was reacted with 3-amino-N-(3-dimethylaminophenyl)-4-methylbenzamide to give the title compound; Mass Spectrum: M+H<sup>+</sup> 424.

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